CANCER RESEARCH

A MONTHLY JOURNAL OF ARTICLES AND ABSTRACTS REPORTING CANCER RESEARCH

VOLUME 3 DECEMBER, 1943 NUMBER 12

The Heterologous Transplantation of Embryonic Mammalian Tissues*

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(Received for publication August 3, 1943)

Several years ago it was shown that mammalian cancers could be readily transferred to animals of alien species by utilizing the anterior chamber of the eye as a transplantation site (6, 7). An interpretation of the significance of this demonstration necessitated a more accurate definition of the limits of heterotransplantability and a series of experiments was undertaken to determine whether the power to grow in a foreign host was shared by other tissues. Benign tumors, normal adult tissue, and normal embryonic tissue have been tested with respect to this property, and while the investigation as a whole remains incomplete the observation that normal embryonic tissue survives heterologous transfer seems of sufficient interest to warrant separate treatment.

The ability to transplant embryonic tissue between species, particularly from man to lower animals, offers a new approach to several medical problems, while the autonomous nature of embryonic tissue, evidenced by such behavior, suggests a biological relationship with cancer and for these reasons this phase of the investigation is reported at the present time.

The extensive literature dealing with the heterologous transplantation of embryonic tissue was reviewed by Bosaeus (3) in 1926, and an examination of subsequent publications in the field does not modify his conclusion that, in the main, such transplants behave exactly as do heterologous transplants of adult tissues. These rapidly degenerate and become necrotic in the alien environment while the new host reacts with a demarcating inflammation and develops a granulation tissue that absorbs or sequestrates the foreign tissue.

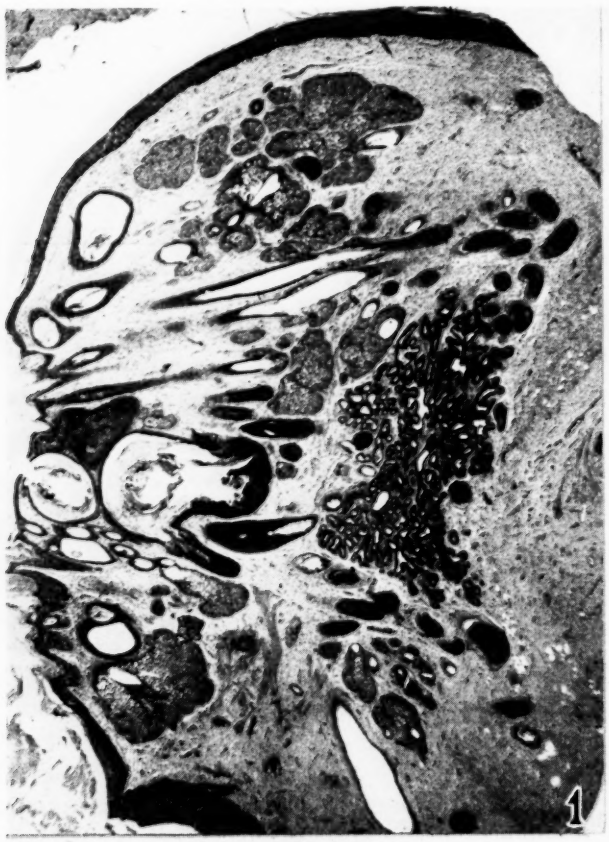
Reports of successful transfers are extremely rare. Fischer in 1882 transplanted pieces of rib and ensiform process from human embryos to the wattles of hens and described some development (4). Saltykow (14) and Petrow (12) also described the growth and development of cartilage in heterologous embryo transfers. Two authors, Belogolowy (2) and Kelling (8–11) stated that in their experiments true tumors followed such transfers. Belogolowy transplanted amphibian spawn heterologously to fish, and both homologously and heterologously to amphibia. The results of heterologous transfer were not different from those of homologous transfer. He asserted, however, that the transplanted cells underwent a sarcomatous change and that the sarcomas eventually killed the animals. His descriptions and pictures were not convincing and the results could not be confirmed by Teutschlaender (15), Piette (13), or Anders (1). The great majority of Kelling's heterotransplants were resorbed and his tumors were too poorly described to be identified as such.

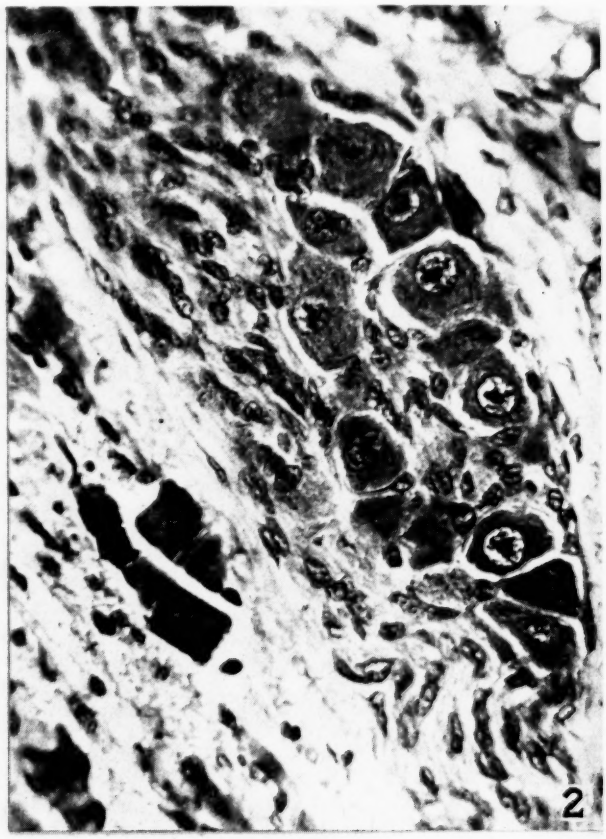
MATERIALS AND METHODS

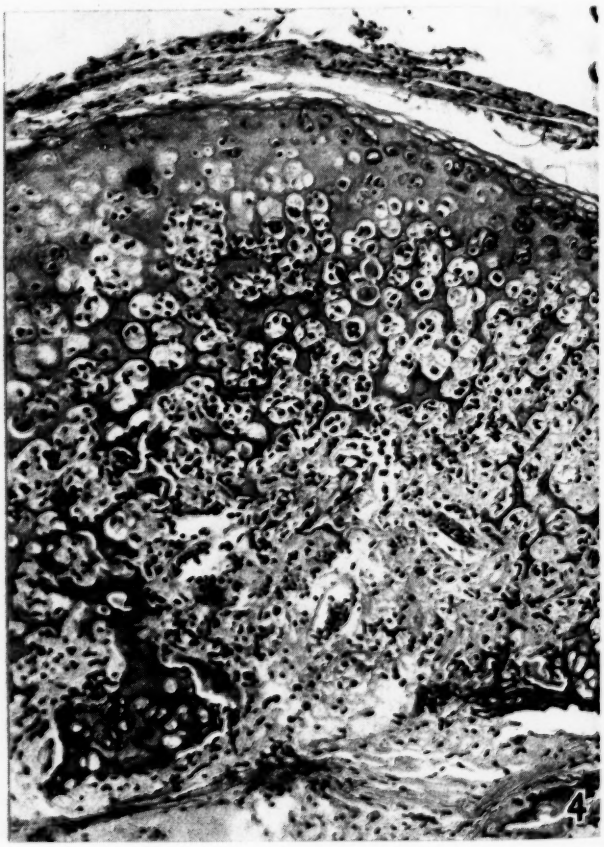
The majority of experiments to be described in this paper were concerned with the transplantation of human and rabbit embryonic tissue to the anterior chambers of the eyes of guinea pigs. In several instances human material was transferred to rabbits' eyes, and in others embryonic mouse tissue was used. The transfer of rabbit embryonic tissue to the testicles of guinea pigs was also undertaken. The experiments were controlled by the homologous transplantation of rabbit embryos, both in the anterior chamber and in the testicle.

The human embryos varied from 2 to 3 months in age and in one instance a 5 month old fetus was used. The former were derived from therapeutic abortions and were transplanted within 2 hours of operation. The latter, delivered by laparotomy, died an hour after operation and was kept in an icebox for 26 hours before transfer was attempted. Rabbit embryos were obtained at various stages of gestation from the seventh to the 30th day.

* This investigation was aided by grants from The Jane Coffin Childs Fund for Cancer Research and The International Cancer Research Foundation.







FIGS. 1–4

In the control homologous experiments, and in guinea pig transfers, whole rabbit embryos as well as embryonic fragments and individual organs and tissues were used. On the other hand, all the human embryos obtained were too large for total transfer and dissected organs and tissues were transplanted.

Both homologous and heterologous tissues were transferred serially in the anterior chamber. Serial testicular transfers were attempted only with homologous material.

The technic of anterior chamber transfer was identical with that employed in the transplantation of tumors (6). Whole tissue fragments were used in testicular transfers and were inserted by means of a trocar after preliminary incision of the skin of the scrotum.

Control Experiments

Heterologous transfers of rabbit embryonic material were controlled by means of homologous transfers of tissues derived from the same embryo or from siblings. Takes occurred in the great majority of cases and neither the frequency of takes nor the manner of growth appeared to bear a relationship to the age, sex, or breed of the host.

The experiments were performed primarily to serve as controls for the heterotransplants, but the results obtained possess independent interest from the viewpoint of teratology and are therefore reported in some detail.

Transplantation of intact embryos.—Embryos obtained between the sixth and eighth days of gestation were usually of a size to allow transfer *in toto*. At this stage, the embryos are extremely fragile and slippery but can be transplanted to the anterior chamber without damage or great difficulty if the corneal incision is made sufficiently small to prevent reflux and a quantity of aqueous humor is allowed to escape before transfer.

If transfer is effected without injury to the embryo a curious phenomenon is observed. After a latent period of 3 to 8 hours during which no change is noted, the embryo begins a rhythmic movement consisting of ventral flexion and extension. The motion is not related to the heart beat, respiratory movement, or other observable activity of the host but appears, on the other hand, to be an independent motion initiated in the embryo itself. It may persist for as long as 24 hours and its cessation is coincident with the appearance of a reddish blush throughout the embryo. The change in color is abrupt and suggests the sudden establishment of blood flow from the host to the transplant.

Growth of the embryo becomes apparent shortly thereafter and proceeds rapidly, so that the chamber may be completely filled within 10 days of transfer. Growth is at first uniform and symmetrical and the embryo maintains its form until, with continued enlargement, it encroaches on the relatively rigid walls of the chamber and is forced into a shapeless, fleshy mass.

If the embryo is injured during the course of transfer, it remains quiescent in the chamber and the movement noted above does not occur. Vascularization appears later and is not uniform or complete, leaving areas that soon become opaque, white, and dead in appearance. Growth is not symmetrical but occurs more rapidly in focal areas and the shape of the embryo is not maintained.

After the chamber has been filled one of two things may happen. Usually the cornea is ruptured by the rapidly expanding tissue and the growth protrudes externally. This is invariably followed by infection and necrosis of the transplant, but even in such cases areas of living tissue may be found as long as 2 months after transfer. In other instances regression follows the filling of the chamber and appears to result from a progressive diminution of blood supply incident to increased intraocular pressure.

Transfer to a new generation of animals may be effected at any time during active growth of the embryo. In several instances tissue fragments removed

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DESCRIPTION OF FIGURES 1 TO 4

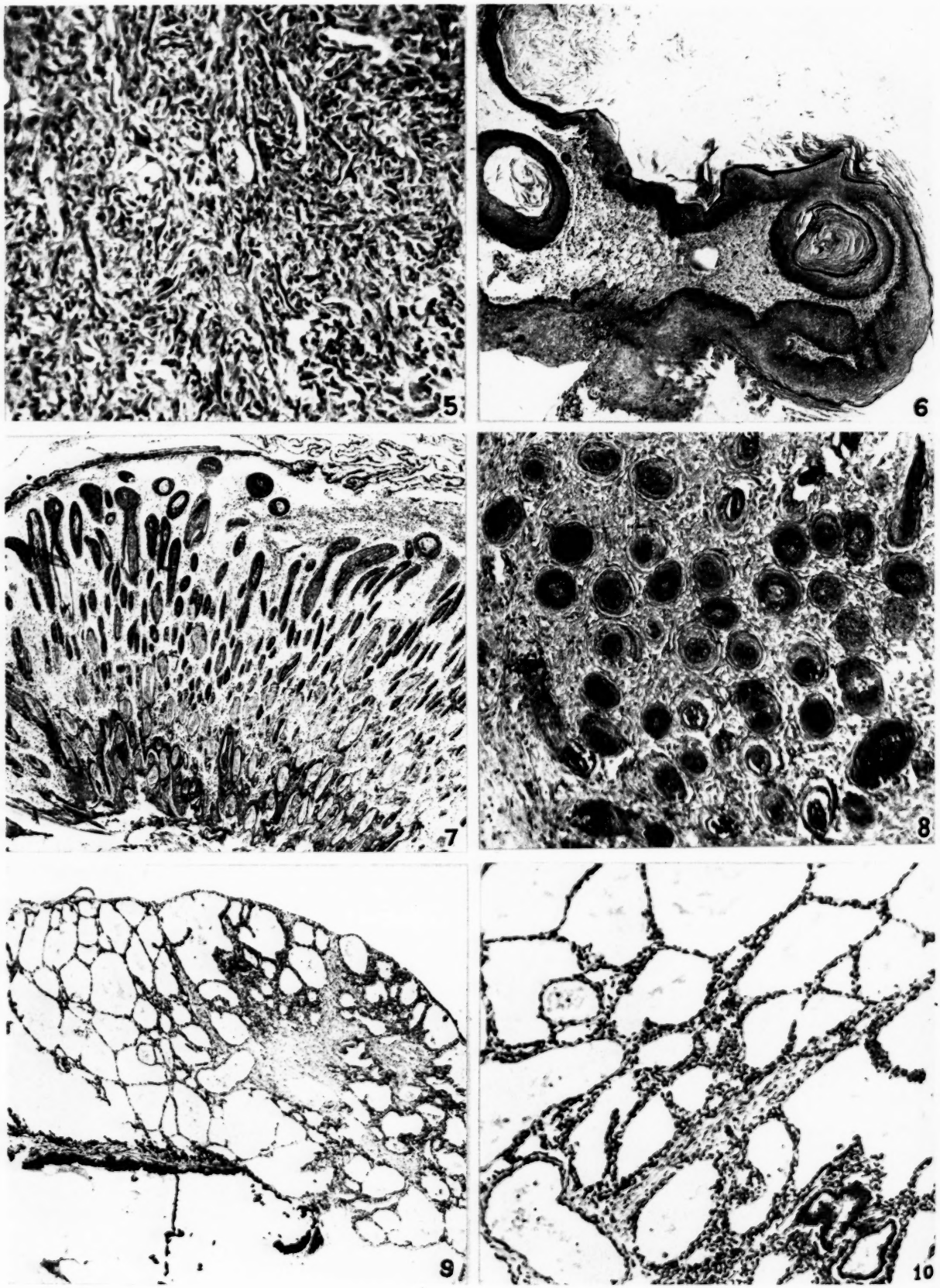
All sections were stained with hematoxylin and eosin.

Fig. 1.—Second generation whole rabbit embryo transplant in rabbit's anterior chamber. The original embryo was obtained on ninth day of gestation. Serial passage was made 40 days after first transfer and the present animal was killed 30 days later. Tissues derived from all germ layers were found in first generation transplant and in different transplants of second generation. This section is made up largely of skin and skin appendages. Mag. × 22.

Fig. 2.—High power view of an area in first generation transplant from which growth in previous figure was obtained. Ganglion cells, nerve and muscle fibers. Mag. × 425.

Fig. 3.—Second generation whole rabbit embryo transplant in rabbit's testicle. The original embryo was obtained on 10th day of gestation. Serial passage was made 30 days after first transfer and the present animal was killed 30 days later. The transplant is made up of cyst lined by squamous epithelium and containing desquamated cells and keratin, a tubular structure lined by columnar epithelium, connective tissue, smooth muscle fibers, and a mass of bone spicules surrounded by osteoblasts. Mag. × 45.

Fig. 4.—First generation whole rabbit embryo transplant in rabbit's testicle obtained 134 days after transfer and showing endochondral bone formation. Mag. × 145.



FIGS. 5–10

10 days after transplantation have been carried through 3 consecutive passages, and there is no reason to doubt the continued success of serial transfer performed in this manner.

The growth rate, as judged by the period of time required to fill the chamber, becomes progressively slower in succeeding generations. As a rule the chamber is filled by the 30th day in second generation animals, whereas 70 to 100 days are required for the same amount of growth in the third generation.

Exceptions are common, however, and the behavior of second generation transplants may be entirely different, depending upon the type of tissue used for transfer. Thus a second generation transfer of tissue made up largely of skin may fill the chamber in 10 or 15 days, while fragments of transplanted cartilage or bone may require 5 or more months to fill a quarter of the space. In one instance a second generation transplant composed entirely of bone merely doubled in diameter during a 250 day period of observation.

Successful testicular transfer may be performed either with embryos obtained directly from the uterus or after a preliminary period of growth in the anterior chamber. A slightly higher percentage of takes follows the latter procedure, but in other respects the results are identical. The transplants grow to a rounded mass approximately 2 cm. in diameter during the first month and show little further increase in size. They remain living, however, and sections obtained 9 months after transfer are made up of healthy tissue. Second generation transfers are successful in a large proportion of cases, but further serial passage has not been attempted.

Upon histological examination the anterior chamber and testicular transplants are found to contain tissues derived from all three germ layers. These are occasionally organized with regard to proper relationships but more frequently there is a lack of orientation and tissues lie in the helter-skelter arrangement characteristic of a teratoma (Figs. 1 to 5).

Tissues are generally well differentiated by the 10th day after transfer, and in some instances maturation in the anterior chamber is more rapid than *in utero*. Thus while rabbit feti are hairless at the end of a 30 day gestation period, skin in the anterior chamber shows pronounced hair growth 10 days after transfer or only 20 days after the beginning of gestation. On the other hand, muscle and other connective tissue elements mature less rapidly, and in many instances embryonic characteristics persist into the third serial generation, or for 150 days after transfer. The point of interest is that in the normal course of events rabbits used for transfer would have been born and would have reached sexual maturity in this length of time.

The transplants in both eye and testicle grow expansively and there is no invasion of normal tissues. The epithelium of the embryo frequently grows over and lines the surface of the iris in a single layer in a manner comparable with that observed in the case of carcinoma transplants, but in the testicle the entire transplant is encapsulated by dense fibrous tissue. Occasionally transplants in both eye and testicle show disorganizing tissue changes highly suggestive of carcinoma or sarcoma (Fig. 5). This resemblance, however, is purely morphological and is not reflected in the biological behavior of the tissue on further transfer.

Transplantation of embryonic fragments.—Embryos obtained between the ninth and 14th days are usually too large for transfer *in toto* and too small for organ dissection. In such instances detached fragments of tissue have been transplanted to the eye and testicle, with a degree of success comparable to that obtained with whole embryos (Figs. 7 and 8).

Transplantation of embryonic organs.—Many individual organs derived from 10 to 30 day old embryos are readily transplantable in whole or in part to the anterior chamber of the eye. At the present time, brain, lung, heart, stomach, intestine, and kidney have been successfully transplanted, but all attempts to transfer liver or glands of internal secretion have failed. Transplantation to the testicle has not been attempted.

Takes are usually apparent by the end of the tenth day in all cases, but the rate of subsequent growth appears dependent on the age of the organ at the

DESCRIPTION OF FIGURES 5 TO 10

FIG. 5.—First generation whole rabbit embryo transplant in rabbit's eye 34 days after transfer. Large areas of the growth showed this disorganizing tissue change suggestive of sarcoma. Mag. × 235.

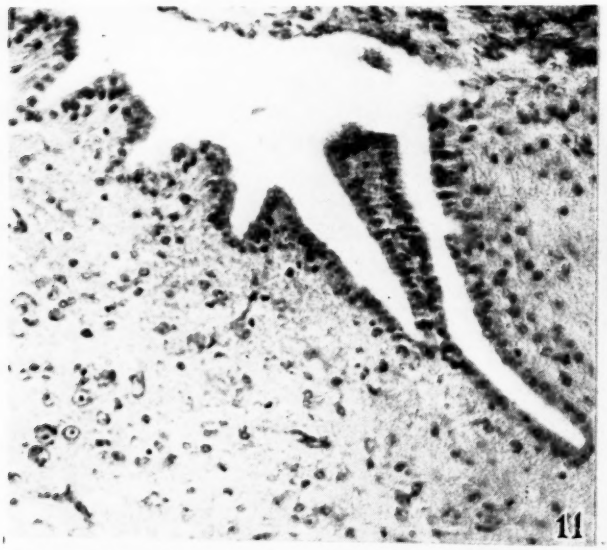
FIG. 6.—First generation anterior chamber transplant of fragment of tissue from midfront region of 14 day old rabbit embryo. The rabbit bearing transplant was killed on 28th day. Hyperkeratotic squamous epithelium with poorly developed rete pegs and several retention cysts. Mag. × 35.

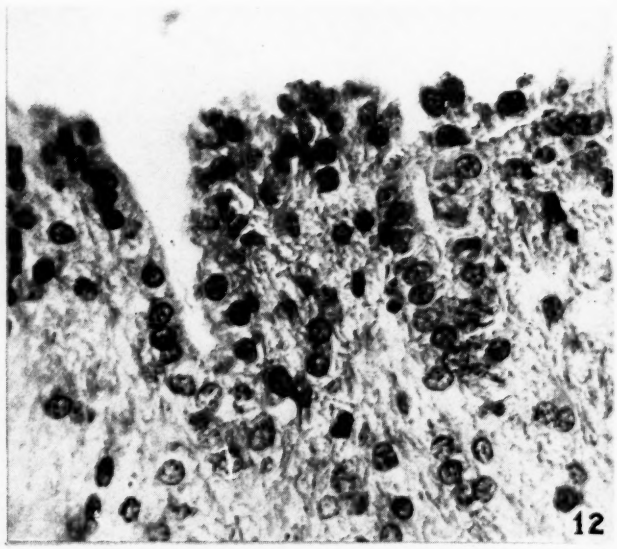
FIG. 7.—First generation anterior chamber transplant of fragment of skin from 20 day old rabbit. Rabbit bearing transplant was killed 36 days after transfer. Numerous well developed hair follicles containing hair shafts. Mag. × 35.

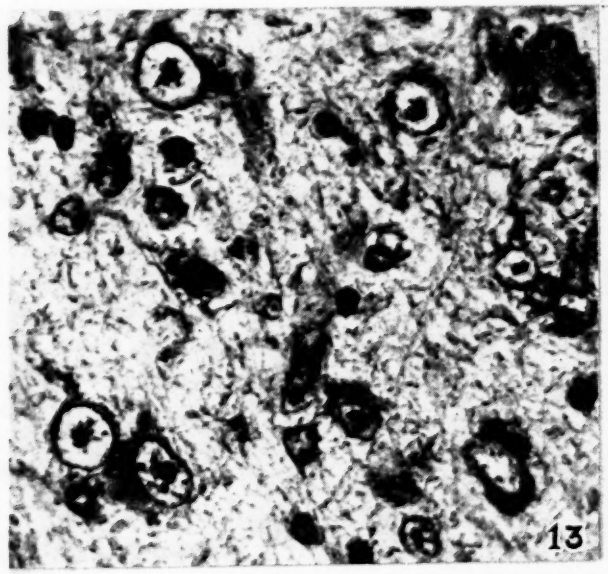
FIG. 8.—First generation testicular transplant of fragment of skin from 10 day old rabbit embryo. Rabbit bearing transplant was killed 26 days after transfer. Numerous hair follicles containing hair shafts. Mag. × 130.

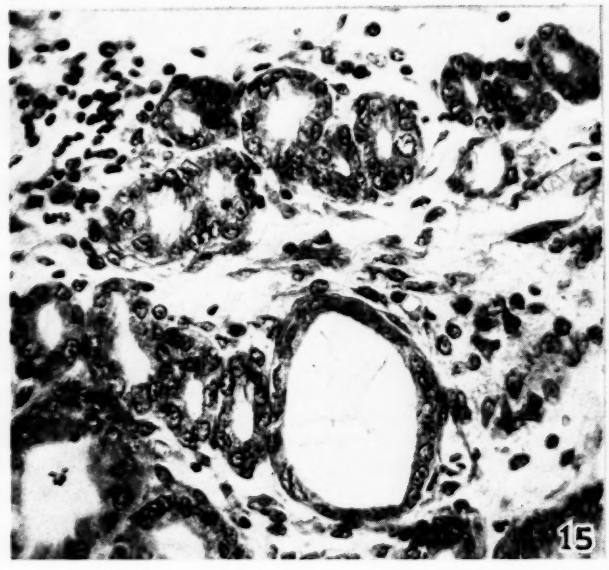
FIG. 9.—Lung transplant from 20 day old rabbit embryo. Rabbit bearing transplant died 36 days after transfer. Well developed, dilated alveoli. Mag. × 45.

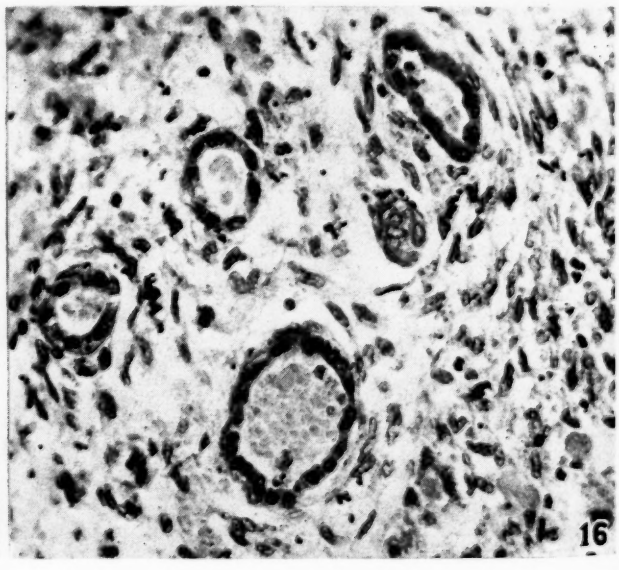
FIG. 10.—Higher power view of previous section showing two small bronchioles in lower right hand corner. Mag. × 150.











FIGS. 11–16

time of transfer. Organs obtained during early uterine life grow rapidly and frequently fill the chamber, whereas fragments of older organs grow more slowly to fill a portion of the chamber and remain without further increase in size for long periods of time.

The more interesting results have been obtained with brain and lung. Curiously, fragments of the cerebral cortex often grow in well formed convolutions and gyri suggesting that such formations are not due to restricted intracranial space, as is generally believed. The transplants reach their maximum size during the first 2 months and then remain without appreciable change. At present several rabbits in the colony bear growths of brain tissue transplanted in May, 1942, more than 14 months ago, and there is no reason to believe that they will not persist throughout the life of the animals. It is significant that despite the long period of anoxemia to which the brain tissue is subjected during transfer histological examination of growing transplants shows numerous healthy ganglion cells in addition to glial elements. It seems highly probable, in view of the known susceptibility of ganglion cells to anoxemia, that the cells seen in transplants represent new elements formed from more resistant neural ectoderm rather than a survival of pre-existing cells (Figs. 11 to 13).

The character of lung transplants varies with the age of the embryo at the time of transfer. Early transplants of tissue obtained during the first half of gestation consist of numerous bronchial buds embedded in loose fibrillar connective tissue with no suggestion of alveolar formation. Later the interstitial tissue becomes fibrotic or may be densely infiltrated with lymphocytes, while the bronchial lumina dilate and the columnar lining cells undergo metaplasia to squamous epithelium. On the other hand, transplants of tissue removed from older embryos show a much closer approach to normal lung structure and consist of relatively sparse bronchi with well defined dilated alveoli. The alveoli contain a pale staining, slightly acidophilic fluid and the dilatation may be so extreme as to suggest emphysema. In fact, emphysematous blebs are sometimes noted on the surface of transplants during gross examination. A further interesting histological feature is the occasional presence in alveolar spaces of large macrophages containing blood pigment that appear identical with the so called heart failure cells of mitral stenosis (Figs. 9 and 10).

Heterologous Transplantation Experiments

The transfer of embryos or of embryonic material from man or from rabbits to the anterior chambers of the eyes of guinea pigs is generally successful, and the growth characteristics of the transplants are not essentially different from those of the control homologous transplants just described.

Transplantation of intact embryos.—The human embryos obtained were all too large for total transfer, and experiments of this nature have been performed only with rabbit material.

Transfer of whole rabbit embryos to pig's eyes is accomplished with considerable difficulty and the embryo is invariably injured during the course of the operation. The rhythmic movement occasionally observed in homologous transplants has not been noted, and the early behavior of the growths is generally comparable with that of injured embryos in the eyes of rabbits.

Vascularization may be delayed for a week or more and is followed by irregular growth in several foci. In approximately 15 per cent of cases regression and death occur after a week of active growth, but in other instances growth is progressive. The transplant enlarges slowly and may fill the chamber in less than a month. Frequently, however, a diminution in growth rate becomes apparent after the third week and 6 months may elapse before one-quarter of the chamber is filled. Serial transfer to the anterior chamber or to the testicle is successful in the great majority of cases.

Upon histological examination the growths are found to contain derivatives of all the germ layers and are identical with homologous embryonic transplants in appearance and structure.

Transplantation of embryonic fragments.—Fragments of tissue from human as well as from rabbit embryos grow and undergo differentiation in guinea pig eyes. The growth rate is slower than in homolo-

DESCRIPTION OF FIGURES 11 TO 16

Fig. 11.—Brain transplant from 14 day old rabbit embryo. Rabbit bearing transplant was killed 144 days after transfer. Portion of the brain tissue surrounding ventricle-like cavity lined by ependyma. Mag. × 235.

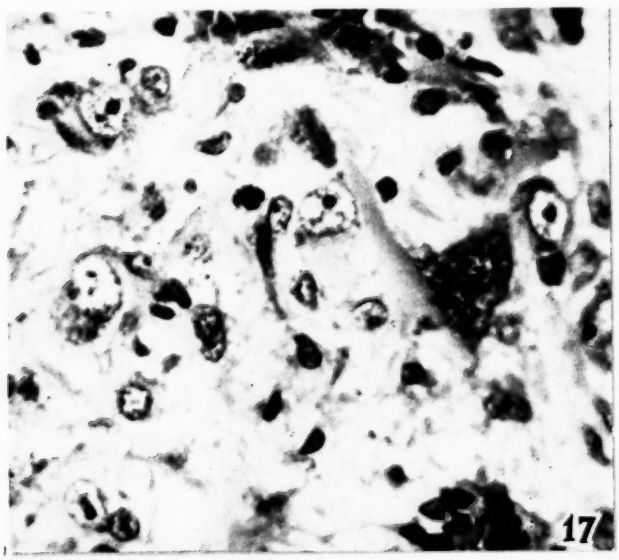
Fig. 12.—Higher power view of previous section to show ependymal lining. Mag. × 475.

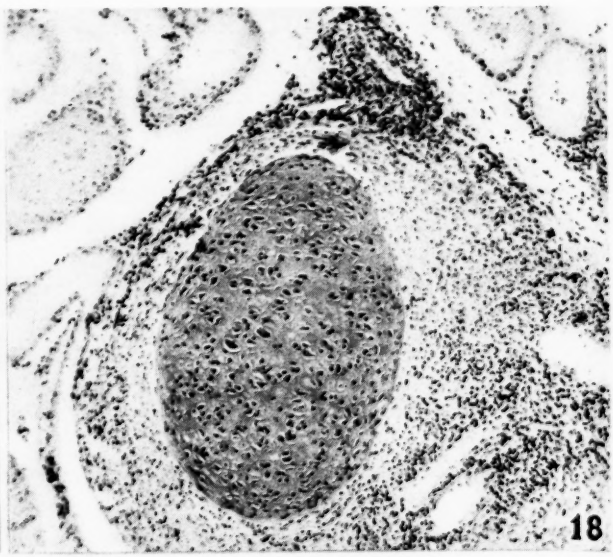
Fig. 13.—Higher power view of Fig. 11 to show ganglion cells. Mag. × 600.

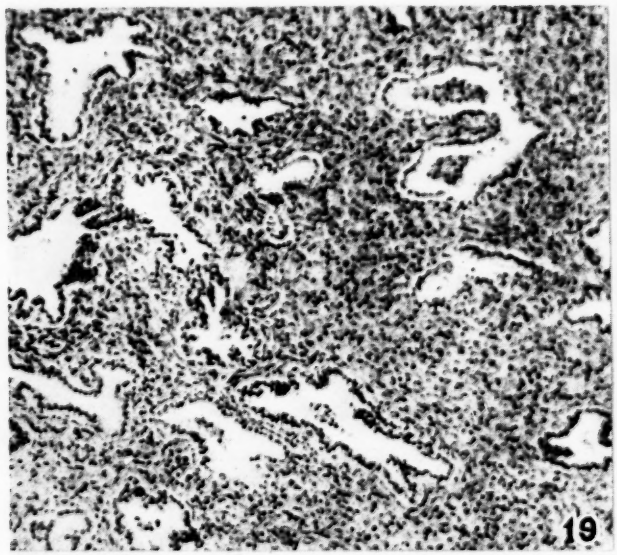
Fig. 14.—Transplant of stomach from 28 day old rabbit embryo in anterior chamber of guinea pig's eye. Guinea pig bearing the transplant was killed 30 days after transfer. Several large cavities lined by mucus-containing cells resembling gastric mucosa. Mag. × 80.

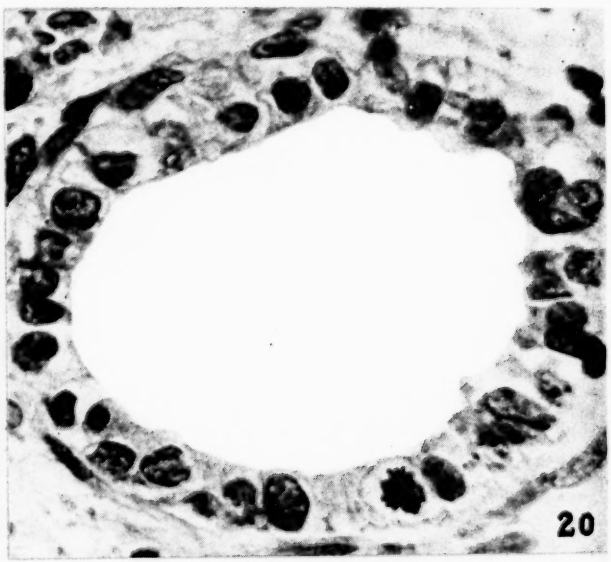
Fig. 15.—Higher power view of different area of preceding transplant showing some of smaller glands. Mag. × 285.

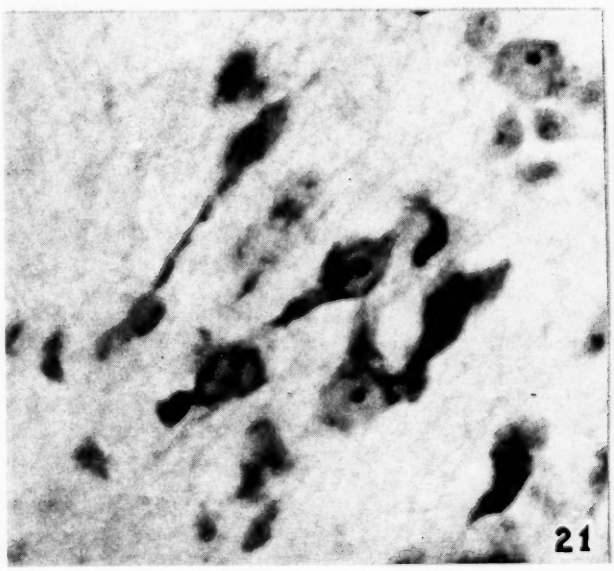
Fig. 16.—Transplant of kidney from 20 day old embryo in anterior chamber of guinea pig's eye. Several epithelium-lined renal tubules in cross section. Mag. × 300.

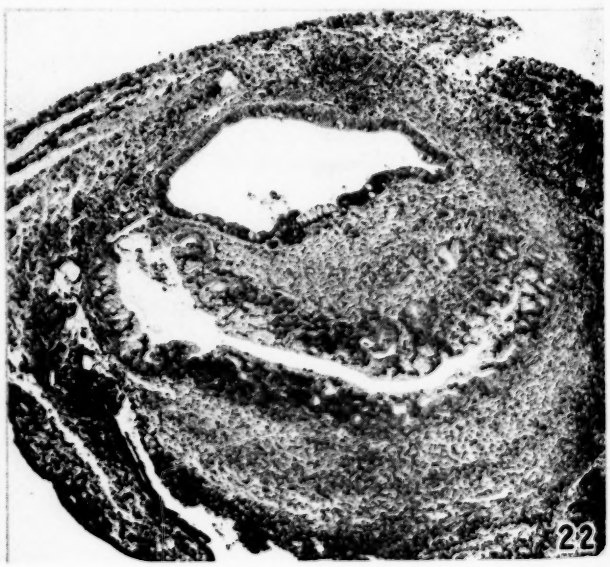












FIGS. 17–22

gous grafts, but in other respects the transplants behave in a similar manner. Fragments made up largely of muscle or connective tissue grow slowly and have not filled the chamber after a 6 month period of observation. On the other hand, cartilage and skin proliferate rapidly and may fill the chamber in 4 weeks.

Serial transfer is usually successful, and at the present time both human and rabbit tissues have been carried through 4 serial passages over a period of 18 months. The rate of growth decreases after continued passage and in the third or fourth generation the transplant may barely double in diameter during a 4 month period.

Fragments of human embryos are also transplantable in rabbits' eyes. Takes are much less frequent and rarely more than 50 per cent of the transplants survive. Growth is rapid, however, and in young animals the chambers may be completely filled in 2 weeks.

and rabbit embryos also grow and differentiate in guinea pig eyes. Transfers of human embryonic organs to rabbit eyes are likewise successful, but the percentage of takes is considerably less than is obtained in guinea pigs.

A variety of organs and tissues including stomach, intestine, kidney, brain, lung, skin, and cartilage have been used with results comparable in all respects with those obtained in homologous organ transplants. However, as in the case of homologous transfers, all attempts to transplant liver or endocrine organs have failed. At the present time the organs of 5 human embryos have been subjected to transfer, and the results obtained in a typical example are shown in Table I. The figures given in this table are also representative of the results obtained with rabbit embryonic organs.

The growth characteristics of human and rabbit tissues are similar, and observed variations appear

TABLE I: THE RESULTS OF TRANSFER OF ORGANS OF A 2 MONTH OLD HUMAN EMBRYO IN THE ANTERIOR CHAMBER OF GUINEA PIGS' EYES

Organ	Skin	Cartilage	Heart	Lung	Stomach	Intestine	Kidney	Brain	Submaxillary Gland	Liver	Adrenals	Thyroid	Gonads
Number of animals	5	4	4	5	2	3	5	6	2	5	2	1	2
Number of takes	4	4	2	4	2	1	2	5	2	0	0	0	0

Testicular transfer of human tissue has not been attempted, but rabbit tissue grows well at this site and persists throughout the life of the guinea pig. Growth is slower than in the anterior chamber and the transplant rarely exceeds a centimeter in diameter after a year of growth.

Upon histological examination early transplants both in the eye and in the testicle are found to contain derivatives of all the tissue used for transfer. Later, however, the more actively proliferating tissues overgrow the transplant and after 4 or more months only skin or cartilage may be present.

Transplantation of embryonic organs.—Organ anlagen and individual tissues removed from human

dependent on the organ used rather than on the species of the donor. Takes are usually apparent within 2 weeks, but occasionally transplants that appear dead suddenly become vascularized and begin to grow as long as 7 weeks after transfer. This behavior is not infrequent in brain transplants, and in one such instance the tissue remained unchanged in the chamber for 3 months before any indication of life was noted. Subsequent growth was extremely slow and at the present time, 16 months after transfer, the transplant occupies less than one-third of the chamber.

As a rule growth is much more rapid and the organ fragment fills a quarter of the chamber by the end of the sixth week. Thereafter growth may cease and the

DESCRIPTION OF FIGURES 17 TO 22

FIG. 17.—Transplant of brain from 11 day old rabbit embryo in eye of guinea pig. Guinea pig was killed on 97th day after transfer. Glia and several large ganglion cells. Mag. × 550.

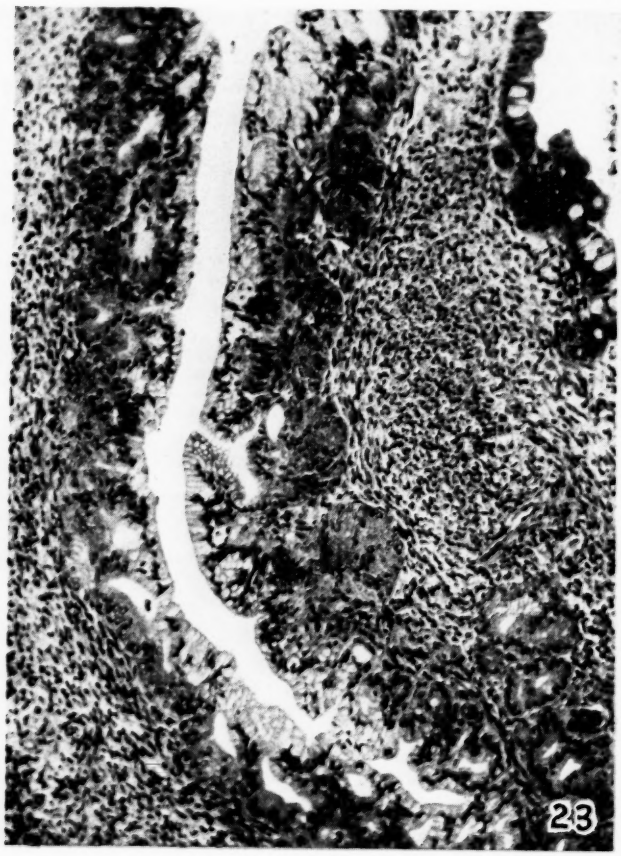
FIG. 18.—Transplant of femur from 15 day old rabbit embryo in testicle of guinea pig. Pig was killed 40 days after transfer. An oval mass of cartilage surrounded by cellular connective tissue. Mag. × 80.

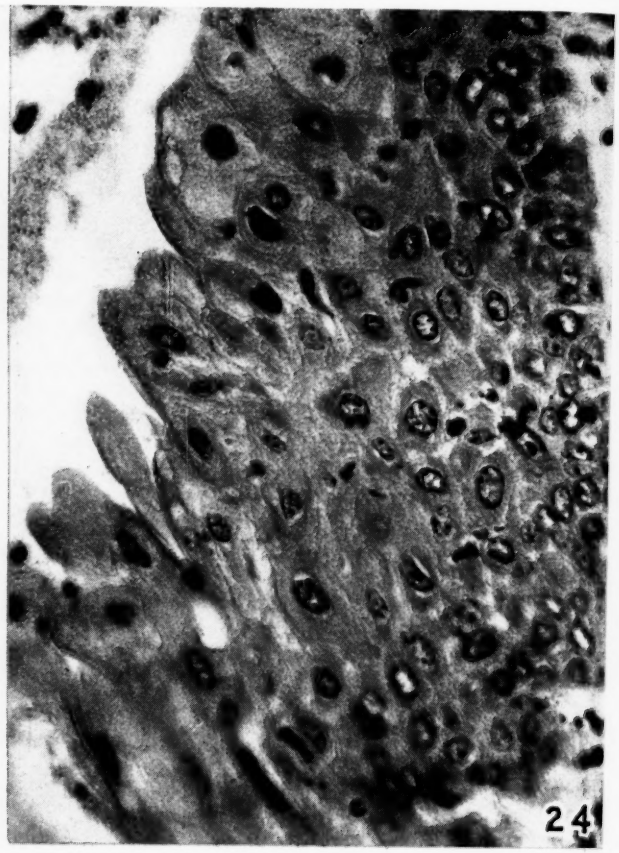
FIG. 19.—Transplant of lung from 3 month old human embryo in eye of rabbit. Rabbit was killed 30 days after transfer. Numerous spaces lined by columnar epithelium embedded in cellular connective tissue stroma. Mag. × 130.

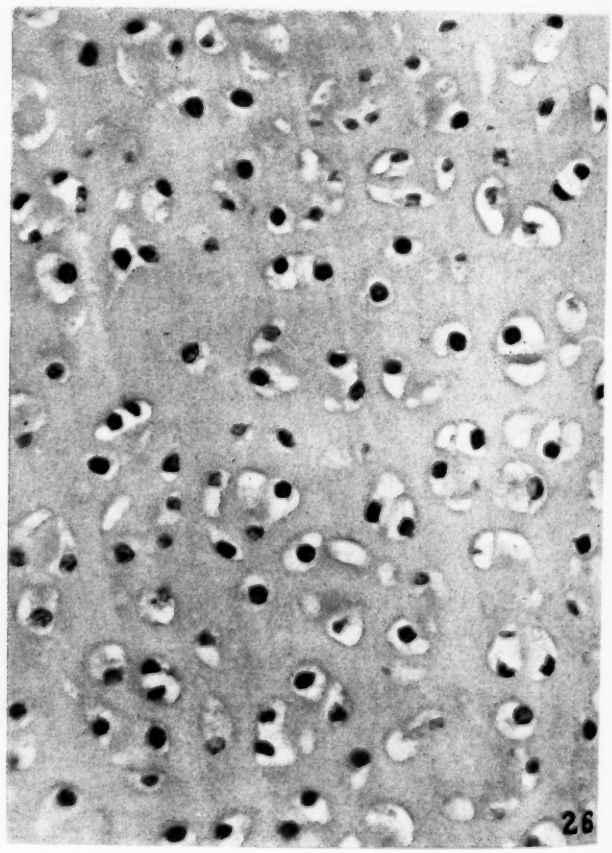
FIG. 20.—Transplant of lung from 2 month old human embryo in eye of guinea pig. Pig was killed on 25th day after transfer. Single bronchiole lined by cuboidal epithelium. Note mitotic figure in lower portion of photograph. Mag. × 750.

FIG. 21.—Transplant of brain from 2 month old human embryo in eye of guinea pig. Pig was killed 133 days after transfer. Several ganglion cells. Nissl's stain. Mag. × 800.

FIG. 22.—Transplant of stomach from 2 month old human embryo in eye of guinea pig. Pig was killed 25 days after transfer. Two cavities lined by gastric mucosa and surrounded by smooth muscle. Mag. × 45.







FIGS. 23-26

transplant persist without appreciable increase in size throughout the life of the animal. On the other hand, growth may continue until the chamber is filled. The largest growths noted in the present series were of brain tissue and of feet.

Rupture of the chamber has occurred in only two instances, and in both of these the transplant consisted of human feet. Here growth was rapid from the very beginning, with elongation of the toes and metatarsals and expansion of the soft tissues. The skin and subcutaneous tissues remained translucent and the progress of ossification could be followed with the naked eye. The shape and structure of the foot were retained until the expanding transplant reached the confines of the chamber and was forced into new growth planes. Subsequently the chamber ruptured in the region of the healed corneal incision, and infection and death of the transplant followed.

Brain transplants appear as translucent, pinkish gray, rounded masses. Fragments of tissue are frequently dislocated from the main transplant during the course of transfer and come to lie in scattered positions over the iris. Growth occurs in these different foci, and with coalescence a single large mass is formed. Occasionally growth ceases before the individual fragments coalesce, and in such instances the iris appears pock-marked with multiple minute particles of brain. Animals bearing transplants of human brain have been watched carefully for abnormalities of behavior or signs of intelligence but to date such have not been forthcoming.

Transplants of lung are notable for their high degree of vascularization and bright red color. The emphysematous blebs occasionally noted in homologous transplants have also been observed in heterologous grafts of rabbit lung, but growths of human lung have not shown this change. Older transplants, more than 3 months of age, often contain grayish opaque areas that may spread to cover the greater part of the growth. Microscopic examination shows that these do not represent necrosis but, on the other hand, an intense lymphocytic infiltration with complete preservation of bronchioles.

Stomach transplants undergo rapid growth to fill a quarter or a third of the chamber in less than a month. Thereafter the outlines of the graft become blurred, the iris reddened, and the cornea clouded, suggesting the possibility of the production of hydrochloric acid with an ensuing inflammatory reaction.

The intestines are not detached from the mesentery before transfer and consequently appear as coiled loops in the chamber. With growth, the furrows between the loops are obliterated and the transplants appear as homogeneous, smooth, rounded masses.

Transplants of liver and of organs of the endocrine system are invariably completely resorbed by the tenth day after transfer.

Histologically the transplants bear a close resemblance to adult organs. Rabbit lung transplants closely resemble homologous grafts with well formed bronchioles and expanded alveoli. Human transplants, on the other hand, consist of numerous bronchi and bronchial buds in a matrix of solid connective tissue and duplicate the so called fetal atelectasis found in stillborn children. Transplants of brain contain numerous glial elements and scattered, well formed ganglion cells. The presence of ganglion cells is especially noteworthy in view of the long period of anoxemia preceding vascularization of the graft. The mucosa of the stomach transplants is made up of mucus-secreting cells, but acidophilic granular cells have not been identified. Numerous tubular elements are found in the transplanted kidney fragments and are believed to represent nephrons. The glomerular tuft is absent, but epithelial invaginations are found that closely resemble Bowman's capsule. Intestinal transplants consist of muscular layers and mucosa surrounding a lumen that is often filled with acidophilic debris (Figs. 14 to 28).

With a single exception all the human embryos used for transfer were obtained during the third month of gestation. The exception consisted of a 5 month old fetus delivered by laparotomy, and the transplantation experiments involved are of added interest in view of the long period of time between death and transfer. The fetus lived for approximately an hour, and after death was placed in an icebox. Transfer of lung and brain was undertaken 26 hours later.

Growth occurred in the majority of transplants and progressed until the animals were killed, 1 month after transfer. Microscopic examination showed that the brain transplants were made up of glial elements; ganglion cells could not be found. Alveoli were not present in the lung transplants despite the fact that expanded air-containing tissue was used for transfer.

DESCRIPTION OF FIGURES 23 TO 26

FIG. 23.—Higher power view of Fig. 22 to show gastric mucosa. Mag. × 150.

FIG. 24.—Transplant of skin from 2 month old human embryo in pig's eye. Pig was killed 30 days after transfer. Stratified growth of epithelial cells. Mag. × 375.

FIG. 25.—Transplant of foot of 2 month old human embryo in pig's eye. Pig was killed 80 days after transfer. Numerous irregularly shaped masses of cartilage bound together by loosely arranged connective tissue. Endochrondral bone formation is in progress in several areas. Mag. × 16.

FIG. 26.—Higher power view of previous section to show character of the cartilage. Mag. × 375.

FIGS. 27–30

On the contrary, the transplants consisted entirely of bronchi and cartilage embedded in loose connective tissue and the resemblance to fetal atelectasis was pronounced.

Attempts have also been made to transfer the organs of several mouse embryos to rabbits and guinea pigs, with results comparable to those described above. Growth is much slower than in the case of rabbit or human transplants and the organs rarely grow to fill more than a quarter of a guinea pig's anterior chamber (Fig. 30).

DISCUSSION

The capacity of embryonic organs and tissues to survive and grow in hosts of alien species is of interest from two separate points of view. The common property of heterologous transplantability accents the biological relationship between cancer and embryonic tissue, while the ability to grow tissues of one species in the body of another offers a new approach to several outstanding medical problems.

The exclusive possession of the power to survive heterologous transplantation shared by cancer and embryonic cells suggests a common attribute that differentiates them biologically from other normal and pathological cells. This peculiar attribute may or may not be an essential factor in the nature of cancer, but in any case it is a property that distinguishes cancer from other pathological cell states and thus deserves consideration and study. The opportunity for investigation of this property is enhanced by the fact that it is shared by a second type of tissue, and comparative studies based on the profound variations in natural history and fate of the two tissues may shed some light on the fundamental nature of cancer.

The growth of embryonic material in the anterior chamber, where its progress may be observed directly with the naked eye or even with the microscope, offers a unique opportunity for the study of morphogenesis. Moreover, the ability to grow human tissues in lower animals renders such tissue subject to experimentation and provides a possible means for the further investigation of a number of human diseases. It is possible, for example, that certain infectious human diseases that have not proved transmissible to other animal species might be successfully transferred to growing transplants of human tissues in the eyes of rabbits or guinea pigs in a manner comparable to that reported by Goodpasture and his associates, who grafted human tissues on the chorioallantois of chick embryos and infected them with viruses (5). In the present instance it is further conceivable that the close association of human and animal tissues in the transplants might result in an adaptation of the infectious agent to the new species.

Of greater interest, in the present connection, is the possibility of studying the action of so called carcinogenic agents on human tissue. The existence of wide variations in the susceptibility of different animal species to carcinogenic chemicals is well established, and a knowledge of the effects of such materials on human tissue would be of considerable importance from the point of view of human cancer. This, obviously, cannot be determined so long as the tissue remains in its natural host, but the tissue can be transferred to a more suitable species and subjected to experimental procedures. Such an investigation is under way at the present time, and while the period of observation has been limited to 14 months it is of some interest that transplants of human tissue impregnated with crystals of methylcholanthrene show no significant variations in growth rate or behavior. Several animals killed after a year's observation have borne transplants that were indistinguishable from sarcoma and carcinoma histologically, but it should be emphasized that the resemblance was purely morphological and was not reflected in biological behavior.

SUMMARY

A series of homologous and heterologous embryonic transplantation experiments are reported. It was found that rabbit embryos, either in whole or in part, could be readily transplanted to the anterior chambers and testicles of other rabbits or guinea pigs. The resulting growths resembled teratomas and could be transferred serially. Similar results were obtained with human and mouse embryonic material transplanted to the eyes of rabbits and guinea pigs. Organ transplants in both

DESCRIPTION OF FIGURES 27 TO 30

FIG. 27.—Transplant of kidney from 3 month old human embryo in eye of rabbit. Rabbit was killed 26 days after transfer. Renal tubule cut longitudinally. Mag. × 250.

FIG. 28.—Higher power view of one extremity of tubule shown in previous figure. Tubule is lined by columnar epithelium and at one extremity epithelium has invaginated to form structure suggestive of Bowman's capsule. Mag. × 625.

FIG. 29.—Transplant of human intestine from 2 month old human embryo in pig's eye. Pig was killed 29 days after transfer. Two cavities lined by columnar epithelium and surrounded by concentrically arranged smooth muscle fibers. In one of cavities epithelium and connective tissue project into lumen in a manner suggestive of intestinal villi. Lumina contain desquamated cells and acidophilic material resembling meconium. Mag. × 150.

FIG. 30.—Transplant from foot of 15 day old mouse embryo in pig's eye. Pig was killed 67 days after transfer. Masses of cartilage arranged in manner of bones of foot. Many areas of endochondral bone formation. Mag. × 40.

homologous and heterologous species underwent differentiation and resembled mature structures. A variety of embryonic human organs including heart, lung, brain, stomach, intestine, and kidney were successfully transplanted but all attempts to transfer liver or the organs of internal secretion failed.

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The Influence of Egg White and Avidin Feeding on Tumor Growth

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(Received for publication June 16, 1943)

The addition of riboflavin and casein to a brown rice-carrot diet significantly protects rat hepatic tissue against injury and tumor production caused by *p*-dimethylaminoazobenzene (2). The further addition of biotin (1) to the diet decreases the amount of protection against the carcinogenic action afforded by the supplements. Experiments done more recently in this laboratory [1] and by the Wisconsin group (3) indicate that other compounds, either members of or closely associated with the B complex group of vitamins, also exert a similar effect.

A study of the biotin content of normal, embryonic, and neoplastic tissues has been reported by West and Woglom (6). The results indicate that the concentration of biotin in neoplastic tissue approximates that of embryonic tissue of the same origin more closely than it does that of corresponding mature tissue. A later report (4) stressed the original observation that the biotin content of neoplastic tissues generally is not abnormally high.

Attempts in experimental animals (7) and the human subject (5) to influence the expected course of a neoplasm by the administration of a diet producing a biotin deficiency were without effect. The results of the following experiments, done on mice bearing spontaneous mammary carcinoma, transplanted sarcoma 180, or Flexner-Jobling carcinoma, are in agreement with these findings.

METHODS

Mice of the strains indicated in Table I and bearing spontaneous mammary adenocarcinomas were fed two different diets producing biotin deficiency. They were permitted to eat as much as they desired. The compositions of the diets were as follows:—

DIET A

Brown rice	70–90%
Egg white	10–30%
Avidin	5–15 units per 3 gm. of diet

DIET B

Sucrose	53%
Egg white	40%
Salts	5%
Cod liver oil	1%
Corn oil	1%
Thiamin	200 gamma per 100 gm. of diet
Riboflavin	500 " " " " " "
Nicotinic acid	1 mgm. " " " " "
Pyridoxin	200 gamma " " " " "
β alanine	1 mgm. " " " " "
Choline	1 " " " " " "
Pantothenic acid	100 gamma " " " " "
Avidin	5–10 units " 3 " " "

The administration of both these diets caused a loss of weight and in 8 to 12 weeks the typical biotin deficiency syndrome. Diagnosis of cancer in most cases was made at first by the aspiration biopsy technic and confirmed at autopsy. Almost all the tumors initially had a diameter of 0.5 to 1.0 cm.

TABLE I: EFFECT OF EGG WHITE-AVIDIN DIETS ON MICE BEARING SPONTANEOUS ADENOCARCINOMA

Strain	Number started	2 week survival	Regression	Recurrence	New tumor	Average survival,* days
EXPERIMENTAL						
Swiss	64	47	6	2 †	5	68
A	18	10	2 †	0	5	30
Paris	9	7	2	0	3	45
Dba	62	33	4 †	0	4	37
C3H	58	33	2	0	13	25
Black	8	6	1	0	1	21
	219	136	17	2	31	36.0
Per cent	100	62	8	1	14	
CONTROL						
Swiss	19	19	0	0	5	77
Paris	2	1	0	0	1	43
Dba	13	9	0	0	4	40
C3H	13	8	0	0	5	32
Black	2	2	0	0	0	20
	48	39	0	0	15	42.4
Per cent	100	81	0	0	31	

* Only those animals surviving more than 2 weeks are included.
† Two tumors in same animal.

[1] Unpublished data.

RESULTS

Among the 48 mice (Table I) on a diet that did not contain egg white or avidin, no tumors regressed and disappeared, and 31 per cent of the mice developed new growths. Nineteen per cent of these animals did not survive longer than 2 weeks.

No significant difference between the results obtained with diets A or B was observed. The data summarized in Table I are a compilation of the results obtained by the use of both diets. Thirty-eight per cent of the 219 mice placed on the high egg white-avidin diets died within 2 weeks. Eight per cent of the initial number of tumors completely regressed, and 14 per cent of the mice developed new tumors while on the deficient diets. There was no significant change in the survival time between the controls and animals receiving the biotin deficient diet. Only those mice that lived longer than 2 weeks are included in the survival time calculation (Table I).

Of the 17 tumors that completely regressed (Table II), 9 were either in mice bearing another one that continued to grow, or in which a new tumor appeared while the animal was still receiving the egg white-avidin diet. A diagnosis of cancer upon biopsy material was obtained on only 2 of the remaining 8 tumors that regressed.

TABLE II: FATE OF MICE IN WHICH ONE OR MORE TUMORS REGRESSED COMPLETELY

Strain	Initial tumor size,* cm.	Time of regression, days	Survival, days	Grew new tumor Remarks
			SWISS	
1	0.7	75	120	Yes
2	0.3	32	153	Yes; also reappeared
3	0.6	15	106	No
4	0.5	15	116	No
5	0.5	75	92	No
6	0.7	23	157	No
			DBA	
1	0.7	15	80	1 of 2 tumors
2	0.4	70	76	1 of 2 tumors
3	0.7	40	78	No
	1.0	65		No
			C3H	
1	0.7	30	35	No
2	1.2	14	20	No. Scab formed
			PARIS	
1	0.5	13	50	1 of 2 tumors; 2 new tumors appeared
2	1.0	28	68	New tumor
			BLACK	
1	0.4	14	30	1 of 2 tumors
			A	
1	0.5	60	150	Yes
	0.3	101		Yes

* Longest diameter.

Of the 17 tumors that completely regressed (Table II), 9 were either in mice bearing another one that continued to grow, or in which a new tumor appeared while the animal was still receiving the egg white-avidin diet. A diagnosis of cancer upon biopsy material was obtained on only 2 of the remaining 8 tumors that regressed.

The Flexner-Jobling rat carcinoma was transplanted into 2 groups of 10 rats each. One group was given a brown rice diet and the other fed this diet supplemented with egg white (20 per cent). The transplants were successful and grew well in 8 of the 10 rats receiving the egg white supplement. Only 5 of 10 transplants in the 10 control rats succeeded.

The mouse sarcoma 180 was transplanted into mice that had received a high egg white diet (30 per cent) for 33 days. This tumor grew as well in the 10 maintained on this diet as it did in mice receiving a normal diet.

Thus in the 3 groups of experiments, with spontaneous mammary carcinoma, transplanted Flexner-Jobling carcinoma, and transplanted sarcoma 180, the tumors grew in most of the deficient animals as well as in the controls, even though the deficient animals were losing weight.

CONCLUSIONS

The administration of a diet rich in egg white and avidin to mice bearing spontaneous mammary carcinoma had no favorable effect on the course of the disease. The successful takes and subsequent growth of the Flexner-Jobling carcinoma and of mouse sarcoma 180 were not inhibited by a diet containing a high level of egg white.

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The Effect of Pyridoxine on Tumor Growth*†

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(Received for publication July 12, 1943)

It has recently been observed that the incidence of liver tumors due to *p*-dimethylaminoazobenzene is much less in rats fed a diet deficient in pyridoxine than in animals on a more complete ration (6). The effect of pyridoxine was evident when the caloric intake of the animals on the two diets was equal, and no similar effect was observed in any of a number of other vitamin deficiencies. Several possible explanations might be offered to account for the suppression of carcinogenesis by the diet low in pyridoxine: (a) the metabolic fate of the azo dye might have been so altered by the deficiency that the effective carcinogenic potency of the compound was reduced; (b) the biochemical reactions by which tumor cells are formed may have been minimized; or (c) tumor cells may have formed as usual, but their subsequent proliferation have been retarded as a result of the dietary deficiency. Accordingly a study was made of the response of a number of different types of tumors to synthetic diets low in pyridoxine. The neoplasms included developing mouse tumors due to the injection or local application of methylcholanthrene, preformed primary mouse tumors, and three types of transplantable tumors. Since the most successful results were obtained with the latter types, the appropriate experiments are described in detail.

Transplantable Tumors

The animals used were adult albino ABC mice and female Sprague-Dawley rats 4 months of age. The mice were kept on screen-bottomed cages in groups of 25, the rats in groups of 15. They were fed synthetic diets either high or low in pyridoxine and the feeding of the special diets was begun 1 month prior to the inoculations. Water was given *ad libitum*, and the ration deficient in pyridoxine was likewise fed *ad libitum*, but the food consumed was measured daily. The animals receiving adequate pyridoxine were then restricted in food intake to those amounts consumed by the animals on the deficient diets, and all animals were weighed at regular intervals. The composition of the diets fed is given in Table I.

After 1 month the rats were inoculated subcutaneously in the abdominal region with the Flexner-Jobling carcinoma, while the mice received either the Yale adenocarcinoma 1 or a fibrosarcoma originally obtained from the ear of a mouse exposed to ultraviolet irradiation. For these inoculations small growing tumors free of external necrosis were removed aseptically, and the tumor was minced and diluted with 2 volumes of 0.8 per cent NaCl. The mice were inoculated with 0.1 cc. of such suspensions, the rats with 0.2 cc. The sizes of the tumors were then estimated at weekly intervals and expressed as the product of length × width × depth in centimeters.

Table I: Composition of Diets

	Mouse diets		Rat diets	
	Low pyridoxine, per cent	Adequate pyridoxine, per cent	Low pyridoxine, per cent	Adequate pyridoxine, per cent
Cerelose	73	73	73	73
Purified casein	18	18	18	18
Salts mixture	4	4	4	4
Corn oil (mazola)	4	4	5	5
Cod liver oil	1	1	..	..
Halibut liver oil			1 drop per rat per week	
	Vitamins in mgm. per kg. of diet			
Thiamine hydrochloride	10	10	10	10
Riboflavin	10	10	10	10
Calcium pantothenate	20	20	20	20
Pyridoxine hydrochloride	0.5	20	0.1	20
Nicotinic acid	30	30	30	30
p-Aminobenzoic acid	10	10	10	10
Choline	30	30	30	30
i-Inositol	100	100	100	100

The B vitamins were thoroughly mixed with 10 gm. of cerelose before incorporation into the rest of the diet.

In general the rats on the diet inadequate in pyridoxine maintained their weights both before and after inoculation with the Flexner-Jobling carcinoma. The

* This investigation was aided by grants from the Jonathan Bowman Fund for Cancer Research and the Wisconsin Alumni Research Foundation. A gift of crystalline B vitamins from Dr. D. F. Robertson, of Merck & Company, is gratefully acknowledged.

† The authors express appreciation to Mrs. Elizabeth Miller for assistance with certain parts of this problem.

animals receiving adequate pyridoxine tended to gain in weight until the tumors attained a large size. Two rats in which tumors did not take were discarded from each group. All other animals on the adequate diet developed tumors, an incidence of 85 per cent, which is approximately the incidence of tumors observed routinely in this laboratory in over a thousand inoculations made into younger animals. In the group on the adequate diet all tumors continued to grow once they were definitely established. The tumor sizes as calculated arbitrarily ranged from 0.75 to 16.55 units at 7 weeks (Table II), average 6.34. During the eighth week some of the large tumors decreased in size, presumably because of a rupture of the wall with loss of necrotic substance.

On the diet inadequate in pyridoxine 5 of the 15 animals failed to develop tumors, and the percentage of takes was 66 per cent. Two of the 10 tumors that became established regressed completely and 3 others decreased in size to virtually negligible dimensions. Of the 5 tumors that continued to grow only 3 reached the average size of the tumors in the control group. The average size of the tumors that still remained at 7 weeks was 2.34 units in the deficient group as contrasted with 6.34 units in the control group. Hence the three criteria employed, percentage of takes, percentage of regressions, and size of surviving tumors, all tended to indicate the presence of fewer and of smaller tumors on the diet low in pyridoxine than on the adequate diet. In other words, more pyridoxine appeared to be needed for the growth of the Flexner-Jobling carcinoma than is sufficient for the maintenance of adult rats for 8 weeks.

Very similar results were observed with two types of transplantable mouse tumors, the Yale carcinoma 1 and the fibrosarcoma. With these tumors both the

TABLE II: THE EFFECT OF PYRIDOXINE ON THE GROWTH OF THE FLEXNER-JOBLING TUMOR IN RATS

	Body weight of rats				Size of tumor (depth × width × length)		
Start of experiment	4 wks.,* gm.	6 wks., gm.	7 wks., gm.	8 wks., gm.	6 wks., cm.	7 wks., cm.	8 wks., cm.
			ADEQUATE PYRIDOXINE				
200	215	230	225	225	0.90	0.75	1.12
220	220	225	227	222	1.50	3.60	2.40
215	205	235	230	230	2.40	5.25	4.20
185	210	215	220	210	3.84	4.20	4.20
195	190	155	157	157	2.00	4.50	4.50
215	215	220	205	205	2.80	6.75	6.00
230	230	240	233	225	3.60	6.00	6.00
235	245	235	245	242	3.00	5.40	6.00
235	245	230	240	240	1.61	4.50	7.00
215	225	225	225	215	1.60	7.00	7.00
235	245	265	270	270	2.40	9.90	7.20
210	215	227	240	230	3.75	8.00	8.00
215	220	235	250	227	5.94	16.55	13.12
Average.. 216	220	226	228	223	2.72	6.34	5.90
			INADEQUATE PYRIDOXINE				
190	185	185	190	195	0	0	0
190	200	205	210	210	0	0	0
225	230	240	235	245	0	0	0
190	190	195	195	200	0.43	0.10	0
190	175	190	180	190	0.72	0.15	0
200	200	210	210	220	0.72	0.15	0.05
200	195	190	190	195	1.20	0.20	0.10
190	185	190	180	185	3.00	0.96	0.22
210	200	212	215	225	0.80	1.00	3.15
190	175	200	200	205	1.80	4.80	3.50
190	185	195	195	195	1.60	6.00	6.00
200	190	210	210	215	1.00	3.24	8.75
225	220	225	235	250	2.40	6.75	9.46
Average.. 201	194	203	202	210	1.05 (1.37) †	1.80 (2.34) †	2.55 (3.90) †

Two animals in which tumors did not take were omitted from each group.
* Inoculated with tumor at 4 weeks.
† Negatives not included in average figure.

percentage of takes and the size of the tumors was greater in the presence of pyridoxine than in its absence, even though the animals on the deficient diet were able to maintain their weights well (Table III). Again, however, there were a few animals in each deficient group in which the transplantable tumors grew as well as in the control group. These exceptional animals may have received more pyridoxine as a result of coprophagy, or they may have been individuals in which the equilibrium distribution of the vitamin between body fluid and tissue protein complex was shifted toward the body fluids. But whatever the explanation, the gross effect of pyridoxine deficiency was a tendency toward reduced tumor growth rather than a complete suppression of it.

Essentially the same experiment was performed under more carefully controlled conditions. Two groups of 25 female mice derived from strain C were fed a basal ration consisting of cerelose 74, purified casein 20, salts 4, corn oil 2, and the following vitamin supplements incorporated as mgm. per kg. of diet; halibut liver oil 10, thiamine 3, riboflavin 6.5, calcium pantothenate 15, nicotinic acid 10, choline 166.5, *p*-aminobenzoic acid 200, inositol 333. In addition one of the diets contained 10 mgm. of added pyridoxine per kg. of ration whereas the other was devoid of added pyridoxine for the first 2 months, after which 1 mgm. per kg. of this vitamin was incorporated in the diet. The animals on the complete diet were restricted in caloric intake to the amounts consumed

Table III: The Effect of Pyridoxine on the Transplantability and Growth of Two Neoplasms in ABC Mice

Number per group	Pyridoxine in diet	Average weight of mice: Start of experiment, gm.	Average weight of mice: Tumor inoculation, gm.	Average weight of mice: 17 days, gm.	Average weight of mice: 24 days, gm.	Average size of tumors (depth × width × length): 17 days, cm.	Average size of tumors (depth × width × length): 24 days, cm.	Average tumor weight, 24 days, gm.	Tumor takes, per cent
				YALE CARCINOMA 1					
25	Low	18.9	20.5	21.1	20.7	0.10	0.35	0.38	80
25	Low	20.8	22.8	23.5	23.3	0.17	0.28	0.47	61.5
25	High	16.6	22.2	22.8	23.3	0.22	0.96	1.09	96
25	High	18.5	26.0	26.0	26.8	0.24	0.78	1.25	88
				FIBROSARCOMA					
50	Low			24.3	23.0	0.45	1.00	1.1	56
50	High			25.7	25.2	1.33	2.54	2.4	76

Table IV: The Effect of Pyridoxine on the Incidence of Tumors in Mice Painted with Methylcholanthrene

Twenty-Five Mice in Each Group

Pyridoxine in diet	Average weight of mice: Start, gm.	Average weight of mice: 2 months, gm.	Average weight of mice: 5 months, gm.	Incidence of tumors at 5 months: Cancer	Incidence of tumors at 5 months: Papilloma	Incidence of tumors at 5 months: Negative	Mice with tumors, per cent
Low	20.9	20.6	22.4	5	3	14	36
High	21.2	20.8	22.1	7	8	9	62

Induced Tumors

Preliminary experiments were performed with tumors induced in mice by the local application of 0.2 per cent methylcholanthrene in dioxane applied to the interscapular region of the back twice a week for 2½ months. Four groups of animals of 15 males or 15 females each were fed the synthetic diets listed in Table I. Eighty-three per cent of those on the diet high in pyridoxine developed tumors as compared to 20 per cent of those on the diet containing no additional synthetic pyridoxine. These experiments, however, were complicated by the unequal caloric intake of the two groups of animals and by the relatively high mortality in the group on the deficient diet. Hence at least part of the inhibiting effect of the deficient diet had to be ascribed to the effect of the lower caloric intake of the animals.

ad libitum by the deficient group. All animals were treated with a solution of 0.2 per cent of methylcholanthrene in dioxane twice weekly for 5 months. Both groups gained in weight over the 5 month period, 0.9 gm. by those receiving the added pyridoxine and 1.5 gm. by those on the deficient diet (Table IV). After 5 months the incidence of tumors averaged 62 per cent in the group receiving additional pyridoxine while only 36 per cent of the group on the deficient diet developed tumors.

In contrast to the results with the epithelial tumors no pronounced effects of pyridoxine deficiency were observed on the development of sarcomas induced by the subcutaneous injection of methylcholanthrene. Experiments were performed with both rats and mice involving a total of approximately 200 animals. An inhibiting effect of a deficient diet was observed only

once under the extreme condition in which rats were depleted of pyridoxine for 5 months before inoculation with the hydrocarbon and continued on the deficient diet for 5 months thereafter. Control animals of similar weight and previously maintained on a grain diet were inoculated with the hydrocarbon and fed a synthetic diet containing high amounts of pyridoxine. In contrast to the rats on the deficient diet these animals continued to grow and their intake of food was approximately 30 per cent more than the deficient animals. Since such a large difference in caloric intake is sufficient by itself to restrict tumor development (2), the observed difference in tumor incidence between these two groups could not be ascribed to pyridoxine *per se*.

DISCUSSION

The results from this laboratory suggest that pyridoxine is necessary for the over-all development both of hepatic tumors due to *p*-dimethylaminoazobenzene (6), and of epithelial tumors due to the local application of methylcholanthrene. The effect appears to be primarily one on the growth of tumors that have already been formed, since the growth rate of several strains of transplantable tumors varies with the amount of pyridoxine ingested. Recently Bischoff and his associates (1) have reported that the growth rate of sarcoma 180 was diminished on a diet deficient in pyridoxine, though not in pantothenic acid deficiency. By a comparison of the caloric intakes of their animals, these investigators concluded that the effect of pyridoxine was specific over and above the effect of caloric restriction. The experiments reported in the present paper are fully in harmony with this point of view. Obviously any effect of diet on preformed inoculated tumors cannot involve the formation of the tumor cell in the first place but rather implies either a change in the nutrition of the tumor itself or a reduced inhibiting influence by surrounding normal cells. Nevertheless, the present experiments do not completely rule out the existence of the former effect. Rats fed *p*-dimethylaminoazobenzene in a diet deficient in pyridoxine exhibit an extremely low incidence of tumors at 6 months (6) and the livers also show only a mild degree of cirrhosis. Since cirrhotic changes are said to precede carcinogenic changes (3) for this type of tumor, one might assume that the deficiency has also tended to suppress precarcinogenic changes, although it is recognized that a few cells might nevertheless have undergone carcinogenesis but have not multiplied sufficiently to be detected at the time of examination.

Tumor experiments involving the deficiency of an essential vitamin are difficult to interpret, since even on a deficient diet the changes in the fluid on which the tumor is nourished are comparatively minor. Adults can maintain their weights for long periods of time in the absence of dietary pyridoxine (5), and, although the growth of younger animals is inhibited, appreciable amounts of pyridoxine can be detected in the tissues after many months of dietary deficiency. A tumor parasitic upon the deficient animal invariably has access to vitamins that were present in the tissues of the host before the deficient regimen was begun. Thus the experimenter is forced to choose between two alternatives. He may deplete each animal of the vitamin for long periods of time prior to the inoculation with the tumor or application of the carcinogen, but this procedure has the disadvantage that the animal is weakened by the time the additional debilitating carcinogenic influence is applied, and thus there is danger that the animals will not survive long enough to develop tumors. Furthermore, the nutritive state of the survivors may be so poor that growth of any kind tends to be suppressed. Since the rate of tumor development is notably sensitive to caloric intake, the control animals on the adequate diet must be greatly restricted in food if they are to receive the same number of calories consumed by the animals on the vitamin deficiency: in other words the "normal" control is also abnormal.

The alternative involves the application of carcinogen to animals not previously depleted, and a small amount of the vitamin may even be added to the deficient diet with the object of maintaining a reasonable survival, a reasonable state of health, and a reasonable caloric intake. Under such experimental conditions extreme qualitative differences between groups can hardly be expected. The numbers and sizes of the tumors observed will differ only quantitatively and to a relatively small degree.

The relative effectiveness of pyridoxine deficiency as compared to deficiencies of other vitamins is not evident from published reports in the literature. Apparently all the B vitamins are present in tumor tissue (7). Biotin has been reported to have a cocarcinogenic effect (2), but further work is necessary to elucidate this observation. Thiamine may be involved in tumor growth (4) but the relative importance of calories and of thiamine *per se* is yet to be evaluated. Dietary pantothenic acid, however, does not appear to be necessary for the growth of transplantable tumors (1). The effect of pyridoxine on experimental tumors can be summed up in the statement that on diets deficient in this vitamin the growth rate of tumors in most animals tends to be diminished.

SUMMARY

1. When the Flexner-Jobling carcinoma was implanted into rats partially depleted of pyridoxine, the percentage of takes was lower, the number of regres-

sions higher, and the size of the tumors smaller than in control animals receiving the same number of calories. Similar results were observed with two types of transplantable mouse tumors: the Yale carcinoma 1 and a fibrosarcoma originally induced by ultraviolet light. A low percentage of tumors in each of the deficient groups grew as well as the average for the corresponding group on the complete diet.

2. The production of skin tumors in mice painted with methylcholanthrene was definitely retarded on a diet low in pyridoxine. This effect, also, was independent of caloric intake. Pyridoxine deficiency appeared to have less effect on the production of sarcomas due to the subcutaneous injection of methylcholanthrene.

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A Free Choice Dietary Study of Tumor-Bearing Rats*

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(Received for publication July 12, 1943)

It is common practice in nutritional studies to feed experimental animals food mixtures made up of protein, fat, carbohydrate, and salts, supplemented with essential dietary factors. This type of diet can be readily adjusted so that it is high or low in any particular constituent. The animal being fed has no choice in the matter and must eat the alimentary mixture as it is presented. Within recent years, however, other dietary investigations have been made in which the animal selects its own diet. The basic ingredients of the ration are the same as in common synthetic diets, but instead of being mixed the materials are all put into separate containers. By eating from the different food cups the experimental animal actually puts together its own diet. Rats selecting their alimentary materials in this manner have been found to grow well and to exhibit normal reproduction (5).

Studies in which the self-selective feeding technic was employed have yielded noteworthy results. Conditions that upset metabolism have been found to alter definitely the appetite of the experimental animal for particular dietary ingredients. Thus after adrenalectomy an animal will ameliorate its condition by seeking and ingesting large amounts of sodium chloride (2). Even more striking are the experiments with diabetic animals. A rat made diabetic by removal of the pancreas and fed the usual type of basal diet will exhibit common diabetic symptoms. If the diabetic animals are put on a free choice diet, however, it is found that they tend to avoid carbohydrate and to eat much more fat than they did before pancreatectomy (6). Furthermore, the dietary selections have pronounced effects on the diabetic symptoms—the polydipsia, increased appetite, and the hyperglycemia either disappearing or being greatly reduced (6). Even normal phenomena, such as pregnancy and lactation, have been found to reflect themselves in the appetite of rats for particular purified foodstuffs when a variety of these is offered. Thus in pregnancy and lactation there is an enhanced appetite for protein and fat but not for carbohydrate (3).

It appeared worth while to apply the free choice type of dietary study to tumor-bearing rats. In this particular study it was hardly to be expected that the tumor itself would be notably influenced by the feeding experiment. On the other hand, it was conceivable that the growth of the neoplasm might alter the appetite of the rats for certain purified foodstuffs, just as the growth of a fetus and lactation alter the appetites of pregnant and lactating rats. Any unusual demand of the growing tumor might be expected to reflect itself in the dietary selections of the host.

EXPERIMENTAL

Pedigreed rats of the pink-eyed agouti hooded August strain were employed in the self-selective dietary experiments. The animals were housed in individual cages, each supplied with five food cups, a water bottle, and a graduated cod liver oil container. The five food cups in each cage contained casein, sucrose, crisco, salts (7), and dried brewers' yeast, respectively. The water-soluble vitamins (other than C, which rats do not need in their diet) were provided by the yeast, and fat-soluble vitamins were furnished by the cod liver oil. Owing to the amount of attention required when the free choice dietary technic is employed, only a limited number of animals was studied at a time. Complete records were obtained for 74 rats, which were investigated in three separate series.

The animals were allowed to subsist on the free choice diet for a week or two before records were kept of the food consumption. This preliminary period permitted the rats to adjust themselves to selecting their own dietary materials from separate containers. After the training period, a weekly record was kept for 8 weeks of the consumption of the various dietary ingredients by each rat. Two weeks after the record-keeping had begun, the animals were divided into two groups. One group of rats (three-fifths of the total number) received tumor implantations and the other did not. In each series the tumor-bearing and the non-tumor-bearing animals were about equally distributed with regard to sex and size. Food consumption and weight records were then kept for an additional 6 week period. It was thus possible, on the one hand, to follow the dietary selection of rats before and after implantation of a tumor, and on the other

* This investigation was aided by the Committee on Scientific Research of the American Medical Association, and by the Detroit Institute of Cancer Research.

hand, to compare the food choices of the tumor-bearing rats with those of the non-tumor-bearing controls.

A mammary adenocarcinoma (R 2426) that arose in the same strain as the animals used in these experiments was employed as a source of material for tumor implantations. The primary tumor was observed February 7th, 1939, in a female rat of the August strain in the Curtis-Dunning rat colony and has been described by Eisen (1). The tumors employed in the present experiment were from the 25th, 26th, and 27th successive transfers. This neoplasm was well suited for these experiments, since it grew moderately fast and yet did not greatly affect the vigor of the animals during the period throughout which food consumption records were kept. Tumor tissue was implanted with the aid of a trocar of wide bore under the skin of the groin on both the right and left sides. In no case did an implanted fragment fail to grow. The average weight of the tumor material at the end of the 6 week growth period was 11.05 gm. per rat.

The growth curves of the experimental groups are given in Fig. 1, which shows that the tumor-bearing rats and the controls grew at about the same rate. The dietary selections of the tumor-bearing group and of the non-tumor-bearing control group are depicted in Fig. 2. It is apparent that the implantation and growth of the carcinoma employed in these experiments did not significantly alter the appetite of the rats for any of the food substances offered. The amounts of the various dietary ingredients consumed throughout the course of the experiment by both the tumor-bearing group of animals and the non-tumor-bearing control group were similar.

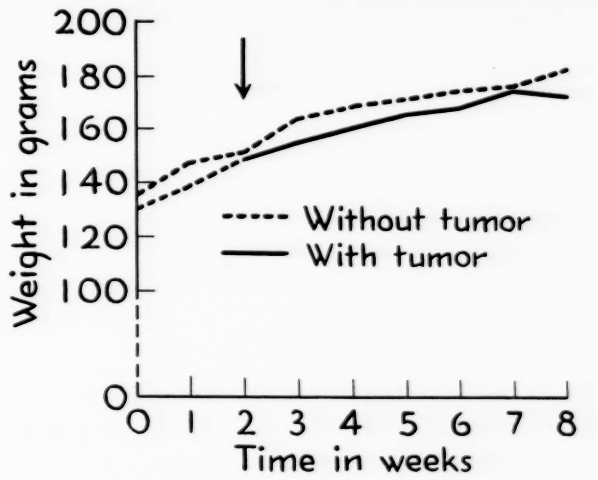

FIG. 1.—Average weight of 30 non-tumor-bearing control rats and of 44 tumor-bearing animals fed a free choice diet. The rats of the latter group received the tumor implantation at the time indicated by the arrow.

DISCUSSION

Free choice dietary studies of pancreatectomized, adrenalectomized, or parathyroidectomized animals

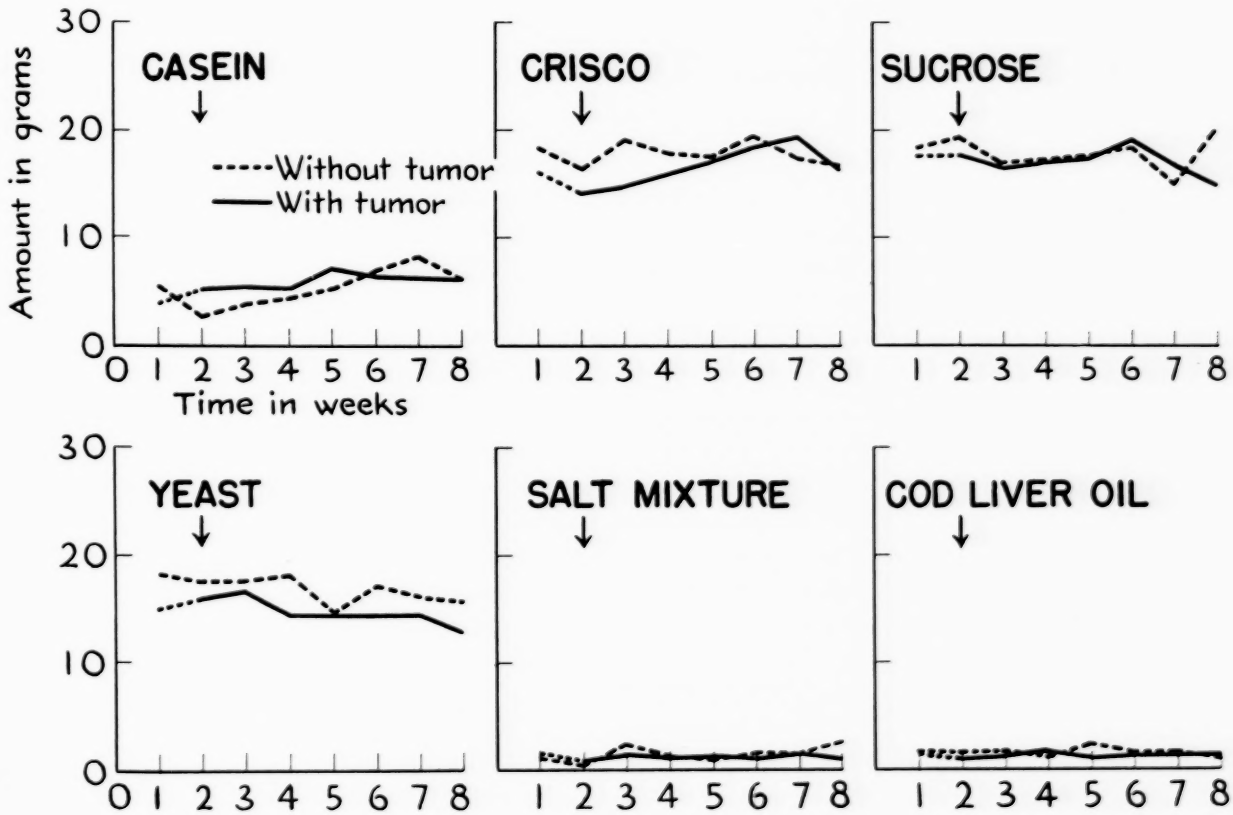

FIG. 2.—Average weekly consumption per rat of dietary ingredients by 30 non-tumor-bearing control rats and by 44 tumor-bearing animals. The tumor was implanted into animals of the latter group at the time indicated by the arrow.

have indicated that the appetite of the animals for particular foodstuffs is altered in a direction that will tend to alleviate the metabolic disturbance, the diabetic pancreatectomized animal choosing fat and avoiding carbohydrate (6), the adrenalectomized animal seeking sodium chloride (2), and the parathyroidectomized animal selecting salts containing calcium (4). Since the dietary selections of rats apparently have a close relationship to the animals' internal needs, it seems reasonable to suppose that if a tumor required an abundant quantity of any particular dietary material this fact would reveal itself in the type of study here reported. The fact that a growing mammary adenocarcinoma (R 2426) in our experiments did not noticeably alter the appetite of the animal for particular unmixed dietary ingredients would seem to indicate that the structural and the energy-providing materials required by this growing neoplasm are not significantly different from those required by the rest of the rat body. Whether studies of other types of growing tumors will yield similar results remains, of course, to be seen.

SUMMARY

The influence of tumor growth upon the nutritive requirements of the host animal was studied by the free choice method of feeding.

The experimental data revealed that the growth of mammary adenocarcinoma (R 2426) in rats did not significantly alter the appetite of the animals for any particular unmixed dietary ingredient. The bearing of this observation on the problem of the requirement of the growing tumor tissue for energy and structural material is briefly discussed.

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Vitamin A and the Toxic Action of Dibenzanthracene on the Tissues

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(Received for publication August 10, 1943)

Having shown the presence of vitamin A in hepatic mitochondria, the authors described the effect of 1,2,5,6-dibenzanthracene on its concentration in these cytoplasmic structures (1), and later supplemented this with a study of the hydrocarbon's action on vitamins A, C, and D in whole liver tissue (2, 3). A review of the data obtained showed that rats were able to withstand the toxic effects of intraperitoneal injections of dibenzanthracene better than rabbits. Thus the average lethal dose of the compound for rabbits with a body weight of 1,200 gm. was about 3 times that for rats weighing only 90 gm. The average amount of vitamin A per liver before treatment with dibenzanthracene was about 2½ times as great in the rabbit as in the rat. This is in line with our finding that vitamin A is concentrated to a greater extent in the hepatic mitochondria of the rat.

It was also noticed during the course of the work that if animals in poor physical condition were purposely selected for analysis of the hepatic tissues the vitamin A content was very much lower than normal; if this type of animal, which ordinarily withstood the effect of dibenzanthracene poorly, was placed on a diet that increased the hepatic vitamin A, much larger amounts of the hydrocarbon could safely be given. These findings suggested the possibility that vitamin A might play a part in protecting the tissues against the injected dibenzanthracene.

The toxic action of the compound is manifested in various ways, one being the failure to gain weight and grow, which ultimately ends in the death of most of the animals (4). Another is its destructive action on the tissues with which it comes in contact. This may be observed in the liver by the occurrence of hemorrhage, degenerative changes in the cells, and necrosis accompanied by reparative processes (6–8). Still another result of its toxic action is the vitamin A-depleting action on the liver tissues (1–3). These findings led to a study of the effect of supplying added amounts of vitamin A parenterally on the severity of these toxic manifestations.

EXPERIMENTAL

In order to study the effect of adding vitamin A on the weight loss caused by dibenzanthracene, 7 groups of 24 rats were fed a commercial chow that had been found adequate by previous test for the maintenance of health and normal growth. The animals of each group weighed from 95 to 110 gm. Each animal of the first group was given a single intraperitoneal injection of 15 mgm. of 1,2,5,6-dibenzanthracene dissolved in 2 cc. of olive oil. The second, third, and fourth groups were given a similar amount of the hydrocarbon in olive oil but various amounts of vitamin A were added in each instance. Thus the animals of the second group were each given a single intraperitoneal injection of 825 U.S.P. units of vitamin A plus 15 mgm. of dibenzanthracene. Each animal of the third and fourth groups received 2,100 and 3,300 units of vitamin A respectively and the usual amount of the hydrocarbon. For purposes of comparison the fifth group was injected with 2 cc. of olive oil alone; the sixth and seventh groups were injected with 1,000 and 5,000 units of vitamin A in 2 cc. of olive oil respectively. The last 3 groups served as controls, no dibenzanthracene having been given to any of these. The vitamin A was a purified concentrate containing 2,000,000 U.S.P. units per gm.; its great potency required the addition of only small amounts in order to obtain the ratios mentioned above. One-half of each group of animals was weighed three times a week at the start and later twice a week. The other half of each group of rats was used for a progressive study of the tissue changes and variations in hepatic vitamin A content. Thus the influence of vitamin A in various amounts was observed on the lack of growth and high mortality as well as on the destructive changes in the liver and depletion of vitamin A brought about by dibenzanthracene. The last two observations were made on animals sacrificed at various intervals during the experiment. For this purpose a number of portions of liver were reserved for histological study and the remainder used for the determination of vitamin A. The sections of liver were

made after imbedding in paraffin in the usual way and stained with iron hematoxylin and eosin. The vitamin A was extracted from the pulped liver according to Moore's method (5) and determined colorimetrically by means of the blue color (Carr-Price reaction) obtained with a saturated solution of antimony trichloride in chloroform. The same color obtained with this reagent and a weighed quantity of biologically standardized vitamin A suitably diluted with chloroform served as a standard for comparison.

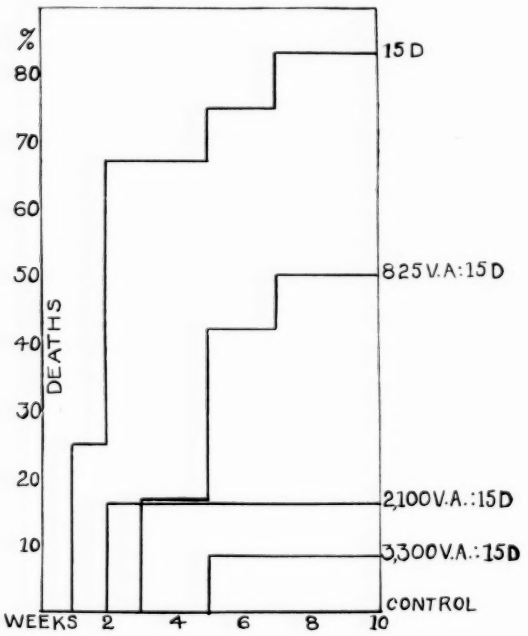


FIG. 1.—The effect of vitamin A on the death rate of rats treated with 1,2,5,6-dibenzanthracene. Control indicates deaths in 3 groups of rats receiving 2 cc. of olive oil alone, 1,000 and 5,000 U.S.P. units of vitamin A respectively; 15 D shows deaths in a group receiving 15 mgm. of dibenzanthracene alone; 825 V.A.:15 D, 2,100 V.A.:15 D, and 3,300 V.A.:15 D refer to deaths in each of 3 groups of rats treated with 825, 2,100, 3,300 U.S.P. units vitamin A plus 15 mgm. of dibenzanthracene respectively.

RESULTS

Fig. 1 shows graphically the effect of different amounts of vitamin A in reducing the number of deaths that ordinarily result from the injection of dibenzanthracene alone.

Fig. 2 shows the change in weight of the various groups. In contrast with the control groups, all of which showed a steady increase in weight, those receiving dibenzanthracene showed a diminished growth rate even in the first week. But whereas the group injected with dibenzanthracene alone showed a persistent failure to grow, the 3 groups with vitamin A added to the dibenzanthracene started to gain weight once more. This was more noticeable in the 2 groups receiving the larger amounts of added vitamin A. The difficulties, however, placed in the way of a resumption

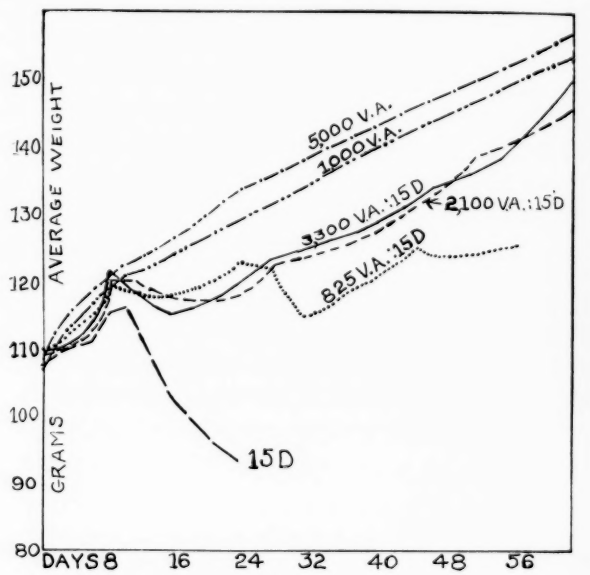


FIG. 2.—The effect of vitamin A on the growth of rats treated with 1,2,5,6-dibenzanthracene. ·—·—·—·—·—·—·—·— 5,000 V.A. and ··—··—··—··—··—·· 1,000 V.A. show growth of 2 control groups receiving 5,000 and 1,000 U.S.P. units of vitamin A respectively; ———————— 15 D indicates change in weight of a group receiving 15 mgm. of dibenzanthracene alone; ———————— 3,300 V.A.:15 D, – – – – – – – – – – – 2,100 V.A.:15 D, and ..... 825 V.A.:15 D refer to growth of each of 3 groups treated with 3,300, 2,100, and 825 U.S.P. units of vitamin A plus 15 mgm. of dibenzanthracene respectively. The average weight of each group has been plotted against the time in days.

DESCRIPTION OF FIGURES 3 TO 6

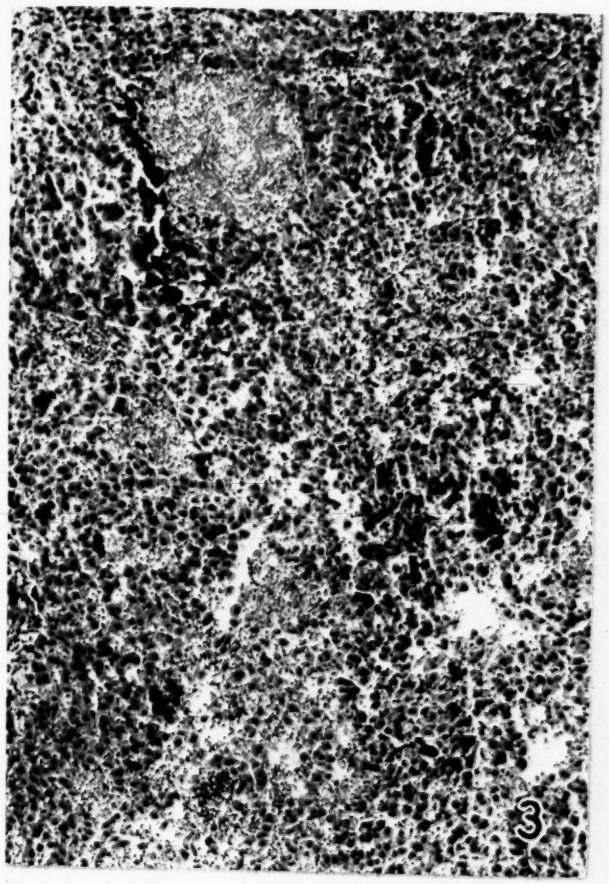
All sections were stained with hematoxylin and eosin

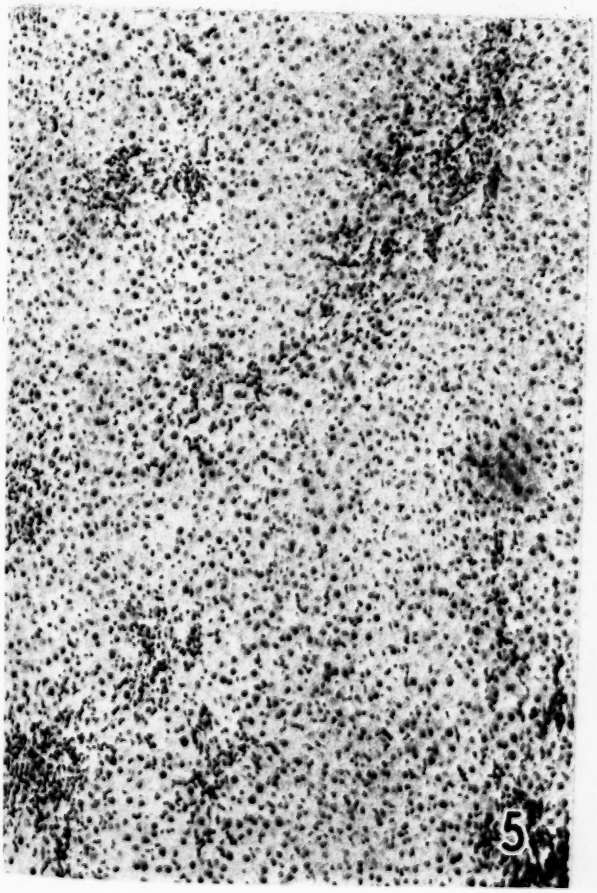
FIG. 3.—Liver from rat 53, 14 days after intraperitoneal injection of 15 mgm. of dibenzanthracene in 2 cc. of olive oil, showing widespread necrosis of liver cells, with considerable congestion and hemorrhage. Mag. × 72.

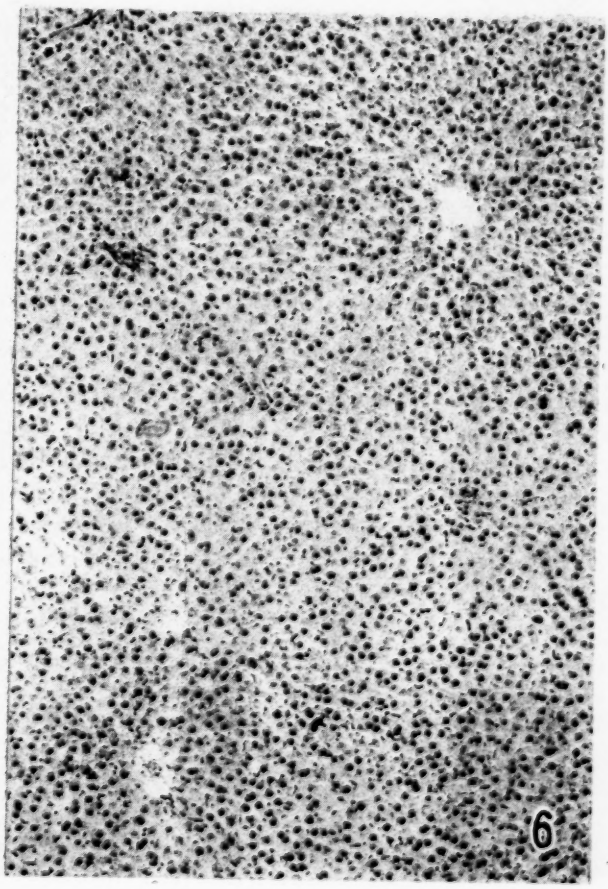
FIG. 4.—Liver from rat 55, 21 days after intraperitoneal injection of 15 mgm. of dibenzanthracene in 2 cc. of olive oil, showing extensive necrosis both about the central vein and peripherally in the liver lobule. Small round cell infiltration into these areas, particularly in lower half of section. Somewhat less congestion. Mag. × 72.

FIG. 5.—Liver from rat 5, 77 days after intraperitoneal injection of 15 mgm. of dibenzanthracene in 2 cc. of olive oil, showing the repair that took place by regeneration of liver cells, and a residual fibrosis. Mag. × 72.

FIG. 6.—Liver from rat 30, 19 days after intraperitoneal injection of 15 mgm. of dibenzanthracene plus 2,100 U.S.P. units of vitamin A in 2 cc. of olive oil, showing the protection afforded the liver cells against toxic action of dibenzanthracene by the addition of vitamin A. Mag. × 72.







FIGS. 3–6

of normal growth by the presence of the hydrocarbon in these groups can be seen in the growth curves.

At autopsy animals receiving dibenzanthracene alone showed noticeable enlargement of the liver. During the first week the transudates observed in the peritoneal cavities contained globules of the oil that had been used as a solvent for the hydrocarbon. In the second and third weeks numerous adhesions had developed between the liver and surrounding tissues, but particularly between the liver and diaphragm. Precipitation of some dibenzanthracene and deposition of fibrin could also be seen on the liver, especially on the diaphragmatic surface. Under the experimental conditions imposed ascites was not a prominent finding. None of the animals of the control series showed any pathological changes although tiny globules of olive oil could be demonstrated in the peritoneal cavity for a week.

Microscopically the hepatic lesions seen in the group treated with dibenzanthracene alone were characterized by numerous and diffusely scattered foci of necrotic liver cells. These areas appeared opaque and contained nuclear debris. Where the liver cells had not disintegrated the cytoplasm appeared homogeneous, having lost its normal granular structure. This degenerative change in the cytoplasm was so distinctive that it enabled one in most instances to differentiate the liver sections of the dibenzanthracene-treated group from both normal controls and those treated with dibenzanthracene plus vitamin A. Congestion was invariably observed and extravasation of blood occurred in the larger necrotic areas.

Repair processes were initiated by small round cell infiltration into the necrotic areas. As time progressed fibroblasts made their appearance. Side by side with these changes there was noted an invasion of the necrotic areas by irregular groups of regenerating liver cells finally resulting in an irregular lobular structure in which varying degrees of fibrosis persisted. There was also some proliferation of bile ducts but this was not a prominent feature.

In contrast with these findings all animals receiving dibenzanthracene plus vitamin A showed only slight to moderate enlargement of the liver. Adhesions between the liver and surrounding tissues were minimal. There was no ascites.

Microscopically the scarcity of necrotic areas was especially striking. In addition the cytoplasm of the liver cells retained its granular structure. In some instances slight congestion was evident, but this was no greater than that observed in controls treated with large amounts of vitamin A alone. None of the control groups showed necrosis.

Table I correlates these histopathological findings with the hepatic vitamin A content. During the first 23 days following injection of 15 mgm. of dibenzanthracene alone there was notable destruction of liver cells. During the next 52 days necrotic areas in smaller numbers were still present in all livers examined. No vitamin A was found in the liver during this 85 day period. Not until the next examinations on the 98th day was vitamin A present.

The outstanding difference between the group described above and all 3 remaining groups shown in Table I is the almost complete absence of liver cell necrosis in those 3 that received vitamin A in addition to the dibenzanthracene. However, in these there was no vitamin A found in the livers during a large part of the experimental period. It seems, nevertheless, that the ability to store vitamin A again returned somewhat sooner than in those treated with dibenzanthracene only. This improvement is maintained most consistently in those animals receiving 3,300 units of vitamin A with the dibenzanthracene; the first vitamin A in this group was detected as early as the 46th day and was present in every subsequent examination. In the group treated with dibenzanthracene alone, only 12 per cent of the animals examined showed hepatic vitamin A; in the group receiving dibenzanthracene plus 3,300 units of vitamin A, 37 per cent of the animals examined showed vitamin A in the liver.

SUMMARY

1. The effect of various amounts of vitamin A on the toxic manifestations produced in rats by intraperitoneal injections of 1,2,5,6-dibenzanthracene was studied.

2. The high mortality resulting from dibenzanthracene was lowered successively by increasing amounts of vitamin A.

3. There was a gain in weight in the animals treated with dibenzanthracene plus vitamin A whereas those treated with the hydrocarbon alone lost weight rapidly.

4. The continued destructive action of dibenzanthracene on the liver cells was decreased by the addition of vitamin A.

5. The addition of vitamin A to the injected dibenzanthracene was not able to prevent the depletion of hepatic vitamin A brought about by the hydrocarbon. Those animals that received vitamin A in addition to dibenzanthracene showed the return of vitamin A in the liver sooner than those treated with dibenzanthracene alone.

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TABLE I: EFFECT OF ADDED VITAMIN A ON THE TOXICITY OF 1,2,5,6-DIBENZANTHRACENE

Rat No.	Time after injection, days	Congestion and hemorrhage *	Necrosis †	Vitamin A per 100 gm. liver, U.S.P. units	Remarks
51	7	+	+++	0.0	Treated with 15 mgm. of dibenzanthracene alone
52	10	+	+++	0.0	
53	14	+++	++++	0.0	
85	14	+	++++	0.0	
54	19	+	++++	0.0	
55	21	+	++++	0.0	
3	23	+	+++	0.0	
4	25	++	+	0.0	
87	31	+	+	0.0	
88	40	+	+	0.0	
45	51	+	+	0.0	
46	56	+	+	0.0	
5	77	—	—	0.0	
47	85	+	+	0.0	
56	98	++	—	1,660.0	
57	98	++	—	610.0	
20	5	—	—	0.0	Treated with 15 mgm. of dibenzanthracene plus 825 U.S.P. units of vitamin A
21	5	—	—	0.0	
24	7	—	—	0.0	
25	7	—	+	0.0	
28	14	—	—	0.0	
29	29	—	+	0.0	
7	38	—	—	0.0	
36	47	++	—	0.0	
35	57	++	—	0.0	
8	66	—	—	192.0	
9	75	—	—	337.0	
59	78	—	—	0.0	
60	85	—	—	2,100.0	
22	5	—	—	0.0	Treated with 15 mgm. of dibenzanthracene plus 2,100 U.S.P. units of vitamin A
23	5	—	—	0.0	
26	7	—	—	0.0	
27	7	—	—	0.0	
11	14	++	—	0.0	
30	19	—	—	0.0	
37	25	—	—	0.0	
31	35	—	—	3,323.0	
32	50	+	—	0.0	
33	66	+	—	56.0	
12	78	—	—	530.0	
13	94	—	++	0.0	
14	100	—	—	4,860.0	
15	100	—	—	680.0	
89	7	—	—	0.0	Treated with 15 mgm. of dibenzanthracene plus 3,300 U.S.P. units of vitamin A
90	14	—	—	0.0	
91	14	—	+	0.0	
92	20	—	—	0.0	
93	24	+	++	0.0	
94	31	—	—	0.0	
95	38	—	—	0.0	
96	40	—	—	0.0	
97	41	—	—	0.0	
98	45	—	—	0.0	
61	46	—	—	356.0	
63	56	—	—	445.0	
16	78	—	—	510.0	
17	84	—	—	540.0	
18	97	—	—	720.0	
19	98	—	—	846.0	

* Congestion and hemorrhage varied from engorgement of vessels represented by +, to large extravasations of blood into the necrotic areas represented by +++.

† The amount of necrosis in the liver sections has been indicated as follows: ++++ represents maximal destruction of tissues for this experiment and involves 40 to 50 per cent of the liver section; lesser degrees are represented by +++, ++, and +, the last amounting to about 5 per cent. No change is indicated by —.

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A Technic for the Production of Hypothermia in Albino Rats

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(Received for publication June 28, 1943)

Bischoff (1) recently described the conditions necessary for the production of hypothermia in mice. Accepting the limitations of the production and maintenance of hypothermia in mice, as described by him, we wish to suggest that the albino rat may be a more suitable animal for the study of the effects of hypothermia on neoplasms. We have produced hypothermia in hundreds of rats during the past 5 years and have found it possible to depress the body temperature to values between 25° and 30° C., as measured high in the colon, and to maintain this low body temperature for a week or longer. There is a certain amount of individual variation in the response to this treatment; some rats can be kept with body temperatures below 25° C. for this period of time, whereas others can be kept below 30° C. for similar periods only with constant attention. Intermittent hypothermia, in which the body temperature of the rat is reduced for as long as 10 hours daily, may be continued for much longer periods.

We have used several different antipyretics in conjunction with exposure to environmental temperatures of 2° to 8° C. to induce hypothermia. Amidopyrine is satisfactory. Routinely we have used a 1.5 per cent aqueous solution of the sodium salt of 1,5-diphenylpyrazoline-3-carboxylic acid, given intraperitoneally in doses of 200 mgm. per kilogram of body weight. For most of our work, however, because we wished to avoid the possibly complicating effects of drugs, we have induced hypothermia by wrapping the thorax and abdomen of the rat with adhesive tape tightly enough to decrease the frequency and amplitude of the respiratory movements. This has the twofold effect of diminishing the oxygen available to the tissues and of building up the carbon dioxide in the blood. Gellhorn (2) has shown that rats breathing an atmosphere low in oxygen and high in carbon dioxide suffer a fall in body temperature, which is particularly pronounced when the environmental temperature is low. Two of us (3) have shown that in the blood of wrapped rabbits and rats the oxygen content falls and the carbon dioxide content rises during the onset of hypothermia. This suggests that the cause of hypothermia in our experiments and in those of Gellhorn is the same.

The details of the wrapping technic are as follows: A small cloth laboratory towel is folded lengthwise through the middle. The rat is placed inside between the halves, with the head inward at right angles to the fold and the animal is rolled tightly in the towel. A paper hand towel is then wrapped around the cloth towel and finally adhesive tape is applied tightly around the paper towel. This last is the critical step. It is only with experience that the operator learns how tightly the tape must be applied to produce the desired results without injury to the animal. A small hole cut in the cloth towel near the nose of the animal prevents suffocation. It is usually necessary to muzzle the rat to keep it from chewing the adhesive. A muzzle made of soft iron wire may be fastened to the wrappings by means of adhesive strips, or a strip of adhesive tape may be so applied as to hold the mouth shut without interference with breathing. The wrapped animal is then exposed to a low environmental temperature and the body temperature is observed at frequent intervals. The cooling may be very rapid if the wrapping is tight. In numerous instances the body temperature has been depressed in less than 3 hours to values below 20° C. When such temperatures are reached the rat should be removed to room temperature and moved back and forth between the cold room and room temperature as the trend of change in body temperature indicates. If the body temperature falls below 16° C., either the animal is placed in the incubator room at 38° C. or the wrappings are removed; in extreme falls of body temperature the two procedures are used together. Frequently rats that appear to be dead may be revived by this treatment with the aid of artificial respiration.

While hypothermia is being maintained for long periods of time, we use 4 different environmental temperatures; the cold room at 2° to 4° C., an ordinary ice refrigerator at 17° to 19° C., room temperature at 25° to 27° C., and incubator room temperature at 38° C. The animals are shifted among these environmental temperatures as is necessary to maintain

the desired hypothermia. During the first few days the rats may require rewrapping from time to time; finally they lose their resistance to hypothermia and the body temperature responds to changes in environmental temperature in a way that suggests poikilothermia.

We use either a thermocouple or a mercury thermometer of the Anschutz type in taking high colonic temperatures. The Anschutz thermometer is, of course, less critical than the thermocouple but has a low heat capacity, registers quickly, and is completely satisfactory for most work. It has the added advantage of convenience. Either the thermocouple or the thermometer should be inserted to a colonic depth of 9 to 11 cm. in adult rats. There is a gradient of temperature fall from the "high colonic" temperature, with the bulb of the thermometer resting just inferior to the diaphragm, to the "rectal temperature," with the bulb of the thermometer inserted about 2 cm. In 50 determinations on adult rats, during exposure to an environmental temperature of 4° C., and with high colonic temperatures ranging from 20° to 36° C., the mean rectal temperature was 3.5° C. lower than the mean high colonic temperature.

Very young albino rats are unable to maintain normal body temperatures when exposed in individual cages, and without other treatment, to environmental temperatures of 4° to 6° C. The ability to withstand low environmental temperatures is acquired gradually in growing rats and is complete at ages ranging from 60 to 75 days. Healthy young adult rats, on simple exposure at 4° C., show a rise in high colonic temperature of 0.5° to 1.5° C. and maintain this increased temperature indefinitely.

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The Effects of Lowered Body Temperatures on Methylcholanthrene Fibrosarcomas in Rats

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When the work of Fay and Henny (4) and of Smith and Fay (10) on the effect of body temperature on the rate of growth of human tumors first came to our attention we had been engaged for some time in a study of the production of subnormal temperatures in rats. The sodium salt of 1,5-diphenylpyrazoline-3-carboxylic acid caused profound falls in the body temperatures of rats exposed to environmental temperatures of 8° C. (9). Also, extremely subnormal temperatures in otherwise normal and untreated rats were produced by the reduction in the rate and volume of respiration with tape wound around the thorax and abdomen and the exposure of the animals to temperatures of 2° to 6° C. (6). It seemed that these technics might well be applied to the study of the effects of lowered body temperatures on the growth of tumors in these animals. We have described in the preceding paper (7) the methods employed for the production of hypothermia and for the measurement of body temperature in rats.

EXPERIMENTAL

Series I.—Our first series of experiments was of an exploratory nature and will be described briefly. Healthy adult rats of the Yale strain were used; these animals were about 11 months old at the beginning of the experiment. The average weight of the females was 304 gm. and of the males, 440 gm. All the animals were fed *ad libitum* on the stock diet (Purina fox chow). Tumors were induced by single intramuscular injections of 3 mgm. of methylcholanthrene dissolved in 0.25 cc. of corn oil (rats 38, 68, and 71 received only 1 mgm. of methylcholanthrene); the injection mass was deposited approximately 1 cm. within the substance of the posterior femoral muscles of the left midthigh. The treatments about to be described were begun on the 83rd day after injection; at this time the only evidence of possibly developing tumors was one or more small, discrete nodules, usually less than 1 cm. in diameter, at the site of injection.

The rats were divided into 5 groups as equally as possible with respect to the size of the nodules in the thigh muscle. In group I, the control group, there were 15 rats, 7 males and 8 females. These animals received the injection of methylcholanthrene as administered to each animal of every group. They were kept at room temperature (25° to 27° C.) at all times and had body temperatures that ranged from 37.4° to 38.5° C., as measured from time to time. In group II there were 7 rats, 3 males and 4 females. These animals were given the sodium salt of 1,5-diphenylpyrazoline-3-carboxylic acid in doses of 250 mgm. per kg. of body weight. This dose was administered in isotonic solution intraperitoneally either 2 or 3 times a week. This group also was kept at room temperature. The pyrazoline injection produced an average minimal body temperature of 34.8° C., a fall of 3.2° C. below the average initial body temperature. The duration of the subnormal temperature after each injection was 4 to 5 hours. The 7 animals of group III, 3 males and 4 females, in contrast to those of group I, were exposed in individual cages to an environmental temperature of 4° C. at intervals of varying length and received no other treatment. The average minimal body temperature of these animals during exposure to cold was 33.9° C., 4.1° C. below the average initial body temperature.[1] The temperatures of the extremities were, no doubt, somewhat lower. The 7 rats of group IV, 2 males and 5 females, were injected intraperitoneally with the pyrazoline salt and then were placed in the cold room at 4° C. This treatment was given 2 or 3 times a week. The duration of each exposure to cold was limited by the rate of fall in body temperature. When the body temperature of any animal fell below 20° C., that animal was returned to room temprature, as were the remaining animals of the group at the end of 3 hours. In this group the

[1] Strictly healthy rats of this strain and of this age, exposed to cold of 4° C., do not show any fall in body temperature by our technic.

average minimal body temperature was between 24° and 25° C. Group V was composed of 6 animals, 2 males and 4 females. Either 2 or 3 times a week these rats were treated by taping the thorax and abdomen in order to reduce the volume and frequency of respirations. They were then placed in the cold room at 4° C. Although the duration of the exposure of these animals to cold was somewhat less than it was with the rats of group IV, the fall in body temperature was a little greater.

The results of these experiments are summarized in Table I. In this table, "Body temperature" refers to high colonic temperatures (7). The mean rectal temperature was 3.5° C. lower than the mean high colonic temperature in the rats of groups III, IV, and V. The

Table I: The Effect of Intermittent Hypothermia, Induced 2 to 3 Times a Week, on the Growth of Methylcholanthrene Fibrosarcomas in Rats

Group	I			II			III			IV			V		
Number of rats	15			7			7			7			6		
Treatment	Controls			Pyrazoline			None			Pyrazoline			Wrapping		
Environmental temperature	25–27° C.			25–27° C.			3–5° C.			3–5° C.			3–5° C.		
	L	S	M	L	S	M	L	S	M	L	S	M	L	S	M
Hypothermia, hours exposure	None														
Average				16	12	14.6	22	12	18.4	16	6	11.2	13	8	10.3
Total				80	60	72	445	106	332	96	36	67	75	27	46
Body temperature, ° C.															
Mean	Normal			36	37	36.7	36.5	32	35.5	28	27	27.8	25	25	25
Minimal	"			34.5	35	34.8	35.1	27.8	33.9	17.9	20.8	19.6	15.2	18.5	17.7
Tumor onset, day postinjection	112	112	135	151	112	128	112	100	119	104	95	98	90	100	111
Death of rat, day postinjection	155	151	178	225	134	172	176	121	170	149	108	129	156	115	146
Rat survival, days after tumor onset	43	39	43	74	22	44	64	21	51	45	13	31	66	15	35
Tumor size, gm.	480	15	161	362	13	132	568	4	198	204	1	77	148	3	52
Tumor growth per day, gm.	11.1	0.39	3.7	4.9	0.59	3.1	8.1	0.2	3.8	4.5	0.1	2.5	2.2	0.2	1.3

L refers to the rat having the largest tumor in the group.
S refers to the rat having the smallest tumor in the group.
M refers to the mean values for all the rats.

of 130 days. In these three groups there was no significant difference in the rate of tumor growth or in the time of survival of the rats. In group IV, the members of which received the pyrazoline and cold treatment, the time interval was 85 to 104 days, with an average of 98 days, 32 days less than the average in the first three groups.

There was a considerable difference in the final size of the tumors; some of them became very large. At the time of death the estimated weight of the tumor of rat 72 (group I) was 426 gm. or 74 per cent of the total body weight, and that of rat 81 (group III), 568 gm. or 77 per cent of the total body weight. The tumors of these 2 rats grew at average rates of 11.1 gm. and 8.1 gm. per day for 43 and 64 days respectively.

"Tumor size" was estimated on the assumptions that the specific gravity of tumor tissue is unity and that the tumors are spheroids. Neither assumption introduces serious error. The formula for the volume of a spheroid is $4/3\ \pi abc$, in which a, b, and c are each one-half of one of the three axes. By repeated measurements we were able to reproduce estimates of the size of the tumors with about 30 per cent accuracy in tumors weighing 20 to 30 gm., and about 20 per cent accuracy in tumors weighing 100 to 150 gm.

In all the animals firm, fairly discrete nodules appeared at the site of injection of methylcholanthrene during an interval ranging from 70 to 130 days. These nodules grew rapidly to a diameter of nearly 1 cm. and then changed very little until accelerated growth began from 10 to 90 days later.

The time interval between the injection of methylcholanthrene and the onset of accelerated tumor growth was approximately the same for groups I, II, and III; the time ranged from 90 to 181 days, with an average

Survival of rats in all groups depended to a considerable extent on the absence of hemorrhage from the site of the tumors. Hemorrhage occurred at various stages in tumor development, and in many cases was unpredictable from the outward appearance of the growth. When the tumors became very large, surface ulcers appeared and usually terminated the experiment by the erosion of a large blood vessel with resulting massive hemorrhage and death.

Nine rats, all of which died by accident, failed to develop tumors; 2 each in groups II, III, and IV, and 3 in group V. The time of death after methylcholanthrene injection ranged from 84 to 134 days. It is possible, therefore, that these 9 animals might have developed tumors if they had lived longer, since the time of appearance of rapid tumor growth after injection of methylcholanthrene, for all the rats, ranged from 85 to 181 days, with an average of 123 days.

Three rats received only 1 mgm. of methylcholanthrene instead of the usual dose of 3 mgm. Two of

these animals did not develop tumors although they lived 114 and 134 days respectively after the injection. The third developed a tumor, which became evident 181 days after the injection. It seems, therefore, that the size of the dose of methylcholanthrene may be one factor in the time required for tumor development.

From the first palpable recognition the small nodules that developed at the site of injection of methylcholanthrene were considered to be tumors; by histologic examination, however, these nodules were found to be composed of inflammatory and granulation tissue, in which occasionally there were small cystic spaces. Neoplastic tissue, with clearly recognizable tumor cells, was evident from the time of the accelerated tumor growth. During investigations now in progress rats will be sacrificed at regular intervals following the injection of methylcholanthrene, in order to detect the earliest neoplastic transformations. Transplant studies of the nodules and tumors will be made in this series of experiments.

Upon gross examination, the incised small nodules appeared either as vaguely outlined fibrous strands or as sharply demarcated grayish white, round or oval nodules; a few contained single cysts, which were either filled with clear yellow fluid or empty and collapsed. The true tumors appeared as grayish white or yellowish white, firm masses that tended to compress the surrounding muscle, without definite encapsulation (Fig. 1). As earlier stated, in many of the rats having the largest tumors there was ulceration of the superficial tissues. On section these tumors revealed large areas of necrosis and larger or smaller hemorrhages.

Microscopic examination of the small nodules revealed typical well vascularized granulation tissue or more cellular fibroblastic tissue, with small numbers of lymphocytes, plasma and large mononuclear cells, as well as a few polymorphonuclear neutrophils, scattered through the tissue. The lining of some of the cysts was bordered with orange-brown globules of hemosiderin. The true tumors were composed of irregular strands and sheets of fibroblastic spindle cells, which extended infiltratively into the adjacent muscular and connective tissue and, in a few places, into the periosteum of the femur. Many of the tumor cells were large and oval, with eosinophilic cytoplasm and large, deeply basophilic nuclei. Some groups displayed more fibrocytic characteristics; other groups were much more anaplastic and had bizarre hyperchromatic nuclei. Some cells were multinucleated; not infrequently the cells contained mitotic figures (Fig. 2). The large necrotic and hemorrhagic areas were conspicuous microscopically. No cells consistent with those of striated muscle origin and revealing striations, suggesting a malignant rhabdomyoma, were detected in any tumor. All the tumors presented the appearance of more or less highly differentiated fibrosarcomas.

Metastatic tumor foci with characteristics similar to those of the primary tumors were found in one rat of group III; this rat showed nothing peculiar during the experiment, but at necropsy was found to have metastases in the lungs, liver, left suprarenal gland, and microscopically in one kidney. Of the total of 90 rats, in our laboratories, that have developed methylcholanthrene fibrosarcomas in the thigh muscle, only 2 others displayed tumor foci—the one in the lungs, the other isolated in the femoral bone marrow. Both these animals died early in the course of the experiments and are not included in this report.

In this entire series of experiments all treatments were begun after nodules had become palpable at the site of injection, but before true tumor growth was apparent. It is evident, then, that none of these treatments prevented the development of methylcholanthrene tumors in these rats. The results with groups II and III show that the tumors in rats subjected to mild intermittent falls in body temperature grow as effectively as those in the untreated animals. The apparent retarding effect of profound intermittent falls in body temperature, manifested in groups IV and V, may be due to the facts that the earlier growth of the tumors in all the groups was slower and that the animals in these two groups did not survive as long as the others.

Series II.—In the second series of experiments the injection of methylcholanthrene was made into rats that were about 6 months old. Treatment with hypothermia, induced with intraperitoneal injections of pyrazoline (rats marked with an asterisk in Table II), was begun 187 days after methylcholanthrene injection; treatment with hypothermia, induced by wrapping, was begun 260 days after injection. In contrast to the rats of series I, all the animals of this series had well developed tumors before treatment was started. The tumors had estimated weights between 23 and 97 gm., with the exception of that of rat 100, which was estimated to weigh 245 gm. After hypothermia was induced the wrapped rats were released and the body temperatures of all the rats were kept below normal continuously by moving the animals to environmental temperatures of 4°, 19°, 27°, or 38° C., as the trend of body temperature change indicated (7). During this treatment frequent measurements were made of body temperature and tumor size. Similar measurements were made in 6 control animals, which were kept at room temperature.

The results of this experiment are summarized in Table II. The figures for "Duration" include the day of the last measurement of tumor size before the death of the animal. The "Mean body temperature" was estimated from frequent measurements made both day

FIG. 1.—Transected, partially necrotic, hemorrhagic, methylcholanthrene fibrosarcoma of left leg, 7.2 × 8.5 × 6.8 cm. at necropsy. Rat 137 (group IV), 149 days postinjection. Mag. × 1.5.

and night during the experiment. Tumors were measured as described for the first series of experiments, with a probable accuracy of better than 30 per cent in these animals. The "Tumor size change" in most of the animals, therefore, is significant. "Tumor growth per day" indicates the rate of change in tumor size and is included because of the difference in the duration of hypothermia in the different animals. "Tumor size change" and "Tumor growth per day" are reported in both grams and percentage because, in comparisons, "grams" used alone gives undue emphasis to the rate of growth in the larger tumors and "percentage" used alone gives undue emphasis to the rate of growth in the smaller tumors.

Immediately after the conclusion of this experiment the control rats listed in Table II were subjected to hypothermia, which was induced in all cases by wrapping the animals and exposing them to temperatures between 3° and 5° C. Intermittent hypothermia was used in the hope that the rats would remain in better general condition because they would eat between treatments. This experiment differed from those of the first series in that hypothermia was induced every day instead of 2 to 3 times a week. It was considered that in this way little time would be permitted between treatments for the resumption of tumor growth. The results are summarized in Table III, which shows that intermittent hypothermia, if repeated at daily intervals, can inhibit growth in tumors of this type. Only rat 78 showed clearly significant tumor growth; and in this animal the rate of growth, as indicated in the last 2 columns of the table, was somewhat depressed from that of the control period (Table II). It may be significant, too, that the mean temperature during hypothermia for rat 78 was the highest of the group. In the other 5 animals the rate of tumor growth was materially less than during the preceding 7 days of normal body temperature (Table II).

TABLE II: THE EFFECT OF CONTINUOUS HYPOTHERMIA ON THE GROWTH OF METHYLCHOLANTHRENE FIBROSARCOMAS IN RATS

Rat	Duration of experiment, days	Mean body temperature, ° C.	Body weight, Total change, per cent	Tumor size			Tumor growth per day,	
				Before, gm.	After, gm.	Change, per cent	gm.	per cent
EXPERIMENTAL RATS								
278	6	32		97	156	+ 61	+ 9.9	+10.1
168 *	6	28	—10	23	32	+ 40	+ 1.5	+ 6.7
0 *	11	30	—30	47	32	— 32	— 1.4	— 2.9
8	6	29	—14	23	14	— 40	— 1.5	— 6.7
79	6	29	—16	36	23	— 37	— 2.2	— 6.2
80	4	27		31	24	— 23	— 1.8	— 5.8
100	1	23		245	270	+ 10	+25.0	+10.0
196 *	2	23	— 7	49	32	— 35	— 8.5	—17.5
65 *	1	21	— 2	80	54	— 33	—26.0	—33.0
CONTROL RATS								
78	7	Normal	—1.7	59	86	+ 46	+ 3.9	+ 6.6
10	7	"	—0.4	50	127	+151	+11.0	+21.5
66	7	"	+3.5	27	50	+ 82	+ 3.3	+11.7
69	7	"	—1.1	59	86	+ 46	+ 3.9	+ 6.6
76	7	"	+2.3	122	158	+ 30	+ 5.2	+ 4.3
1	7	"	—2.6	117	136	+ 16	+ 2.7	+ 2.3

This experiment shows unquestionably that the growth of methylcholanthrene fibrosarcomas in rats may be inhibited by hypothermia. There was no tumor growth during hypothermia, except in rats 100, 168, and 278. There is no doubt in our minds that the tumors of rats 0, 8, 79, 196, and 65 decreased in size during the treatment. But only those of rats 196 and 65 showed a percentage weight loss significantly greater than that of the whole body of the animal. Rats 100, 196, and 65 were kept at lower body temperatures than the others and survived a shorter time. However, the total effect on tumor growth was about the same as for the other rats. This suggests that the lower body temperatures are more effective in inhibiting the growth of tumors. The large tumor of rat 100 probably took longer to cool and may have been cold for a materially smaller proportion of this brief period of hypothermia than the relatively small tumor of rat 65.

DISCUSSION

In the experiments of series I (Table I) the animals were given a balanced diet, which they ate well. In the second experiment of series II (Table III) the animals ate well during the periods of normal body temperature, so that nutrition was probably adequate in the sense of the sufficiency of the nutrients ingested. However, in the first experiment of series II (Table II),

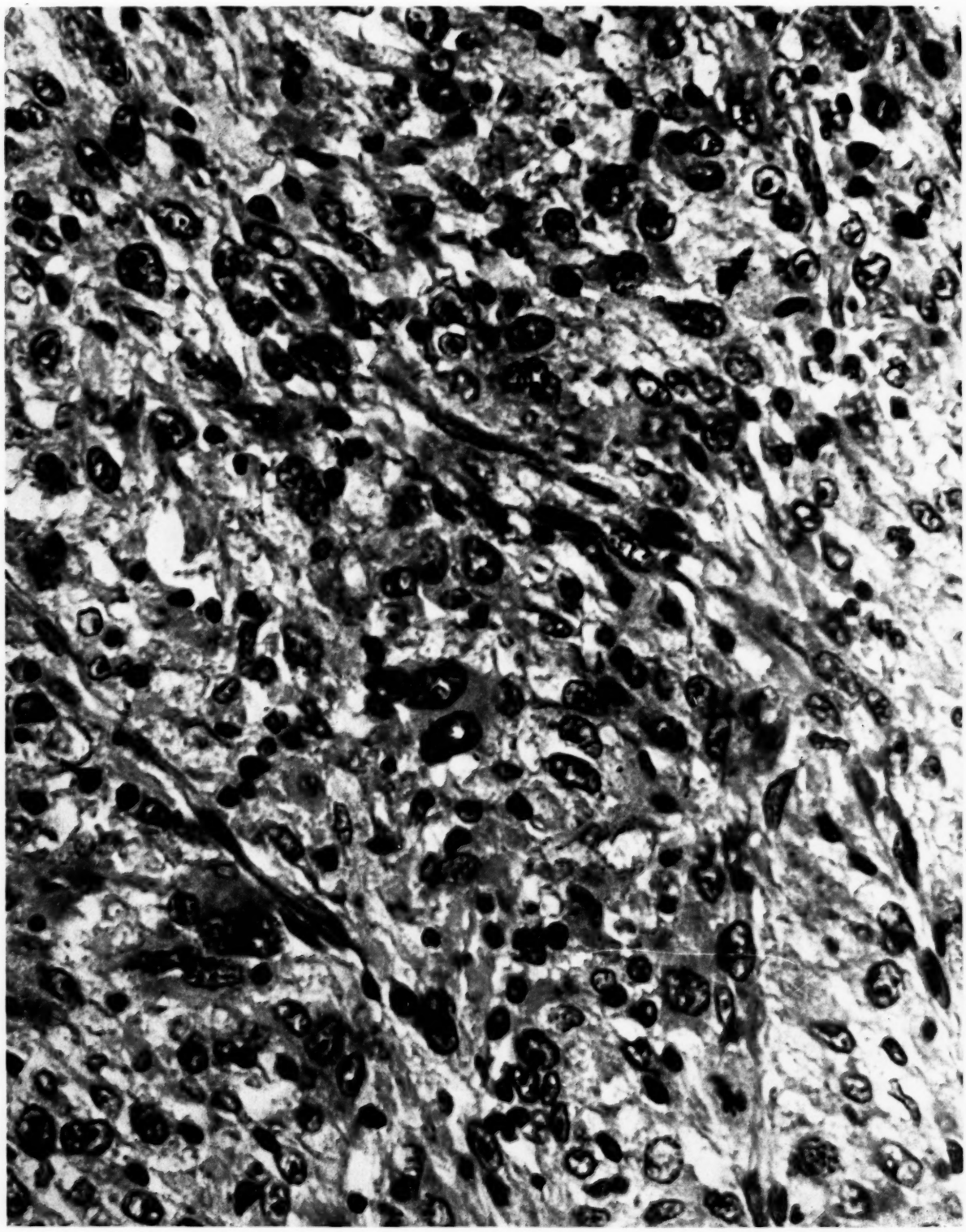

FIG. 2.—Photomicrograph of methylcholanthrene fibrosarcoma, shown in the gross in Fig. 1. Anaplastic tumor cells with bizarre hyperchromatic nuclei and several mitotic figures. Hematoxylin and eosin stain. Mag. × 520.

during continuous hypothermia, the animals ate very poorly although the same balanced diet was offered. It has been shown that poor nutrition, caused by either caloric restriction (12) or a deficiency in certain of the essential amino acids (13), may retard the growth of tumors, and it is probable that inadequate nutrition played a part in producing the results of our experiments. However, although poor nutrition may have been the immediate cause of the retarded growth, cold may have been the indirect cause of both the poor general nutrition of the animals and the poor local nutrition of the tumors. The body temperatures of these animals were measured with the bulb of the thermometer very near the stomach, so that the readings must have approximated closely the temperature of that organ and of the other organs of digestion. During hypothermia, therefore, the food ingested was probably poorly utilized because of the temperature coefficients of the many reactions of secretion, digestion, and absorption.

Table III: The Effect of Intermittent Hypothermia, Induced Daily, on the Growth of Methylcholanthrene Fibrosarcomas in Rats

Rat	Duration of experiment, days	Hypothermia: Total number hours	Hypothermia: Mean temperature, ° C.	Tumor size: Before, gm.	Tumor size: After, gm.	Tumor size: Change, per cent	Tumor growth per day, gm.	Tumor growth per day, per cent
78	12	59	30	86	122	+42.0	+3.0	+3.5
10	12	53	29	127	130	+ 2.3	+0.25	+0.19
66	12	52	28	50	58	+16.0	+0.67	+1.3
69	8	33	28	86	94	+ 9.0	+1.0	+1.2
76	1	4	27	158	160	+ 1.3	+2.0	+1.0
1	12	56	25	136	140	+ 3.0	+0.33	+0.25

Warburg, Wind, and Negelein (14) in a metabolic study of Jensen sarcomas reported that "Even at 20° the fermentation of tumor cells has almost completely disappeared." These authors reported also that in 6 animals sarcomas took an average of 57 per cent of the glucose from the blood passing through them, whereas normal tissues in 6 animals took an average of only 10 per cent of the glucose. Of the glucose removed by the sarcomas, 66 per cent was removed by reactions of fermentation, and 34 per cent by reactions of respiration. In Okamoto's experiments (15) in Warburg's laboratory, Jensen sarcoma cells survived 72 hours without oxygen. Warburg, Wind, and Negelein (14) reported that Jensen sarcoma cells, grown in a medium that had been dialyzed until it was free from glucose, survived for "some time"; but that if the medium was at the same time deprived of oxygen, that is, if both anaerobic and aerobic metabolism was stopped, the tumor cells survived only 4 hours.

If the metabolism of methylcholanthrene fibrosarcomas is comparable to that of Jensen sarcomas, both the anaerobic and the aerobic metabolism of these tumors must have been severely reduced in our experiments. Although no determinations of the oxygen content of the blood were made in these experiments, previously two of us (16) found that blood from the vein at the base of the ear in 17 normal rabbits contained a mean of 17 volumes per cent of oxygen. Blood from the same vein had a mean oxygen content of 9 volumes per cent in 11 of these rabbits when they were wrapped so that the rate and volume of respiration were decreased and their body temperature reduced to 33° C. In the blood of the one rat that we were able to bleed during severe hypothermia (wrapping technic) the oxygen content was 4.6 volumes per cent (20.4 per cent saturation) at a body temperature of 17° C.

A number of factors, active in our experiments, would further decrease the amount of oxygen available to the tissues of animals in the hypothermic state. Britton (2) showed that in 2 cats the heart rate decreased from 260 beats a minute at a body temperature of 39° C. to 120 and 60 beats a minute at body temperatures of 29.3° and 22.4° C. respectively. Tait and Britton (11) reported that in the artificially cooled woodchuck, "with progressive slowing of the heart the blood-pressure steadily falls, to attain all but a zero level when respiration stops." (The operator who attempts to draw blood from a hypothermic animal is convinced that its circulation is very sluggish.) Thus the rate of transport of oxygen from the lungs to the tissues is reduced at low body temperatures. The high affinity of hemoglobin for oxygen at low temperature is well known and has been studied for the hemoglobins of many different animals. There appear to be no data for rat blood at temperatures similar to the body temperatures of our rats, but curves published by Hill and Wolvekamp (5) indicate that rat blood reacts comparably to human blood in this respect. Brown and Hill (3) have published an excellent chart showing the effect of temperature on the dissociation curves of human blood. From these curves it may be estimated that a sample of human blood, when 67 per cent saturated with oxygen, would be in equilibrium with 40 mm. of oxygen at 38° C., with 27 mm. of oxygen at 30° C., and with

16 mm. of oxygen at 20° C.; and that this same sample of blood, when 30 per cent saturated with oxygen, would be in equilibrium with 20 mm. of oxygen at 38° C., with 13 mm. of oxygen at 30° C., and with 8 mm. of oxygen at 20° C. It is evident, then, that the oxygen saturation of 20.4 per cent in the blood of our rat at a body temperature of 17° C. would support only a very low oxygen pressure in the tissues. Krogh (8) has shown that the rate of diffusion of oxygen through muscle and connective tissue decreases approximately 1 per cent for each degree of fall in temperature. Because of this decreased rate of diffusion through tissues at low temperatures, the oxygen delivered by the blood reaches the cells more slowly in animals with low body temperatures. Finally, by direct measurement of oxygen tension in the tissues, Bazett and Sribyatta (1) showed that local cooling decreased the pressure of oxygen available to the subcutaneous tissues of the human forearm, in one subject from 63 mm. of Hg at a skin temperature of 38° C. to 14 mm. at 22° C., and in another from 73 mm. at a skin temperature of 38° C. to 25 mm. at 22° C. All these considerations point to a moderately reduced oxygen pressure in tissues at temperatures of 27° to 30° C. and a greatly reduced oxygen pressure in tissues at temperatures of 20° to 24° C., two ranges of temperature within which most of our experimental work was done.

In the work of Bazett and Sribyatta the reductions in oxygen pressure were 78 per cent and 66 per cent at 22° C.; and these may be considered minimal reductions because the circulation may be regarded as normal, except in the locally cooled area, and because the rate of oxygen supply to the tissues was not as greatly reduced as it would be in general hypothermia. In any case, the mass action of the oxygen is reduced by a value at least of the order of 70 per cent before the temperature coefficients of the oxidative enzymes come into play. This should cause a further considerable reduction in the rate of oxidation. Although the ability of the tissues to utilize the oxygen of the blood is greatly reduced in hypothermic animals, in our experiments the factor of low oxygenation of the blood itself may have been operative only during the induction of hypothermia in the animals continuously treated. In the animals rewrapped daily, the low oxygen content of the blood would further decrease the oxygen available to the tissues, so that hypo-oxia was perhaps as important a factor as hypothermia in inhibiting tumor growth.

SUMMARY

1. Intermittent hypothermia (mean body temperatures of 25° to 36° C.), produced 2 to 3 times a week, did not retard significantly the growth of methylcholanthrene fibrosarcomas in the thigh muscles of rats.

2. Only 2 of 9 rats undergoing continuous hypothermia (mean body temperatures of 21° to 32° C.) exhibited significant growth of methylcholanthrene fibrosarcomas. In 5 of these rats the size of the tumor decreased more than 30 per cent during the treatment.

3. Intermittent hypothermia (mean body temperatures of 25° to 30° C.), produced daily, depressed the rate of growth of methylcholanthrene fibrosarcomas in all but 1 of 6 rats.

4. Tumor growth was retarded more effectively when the hypothermia was severe (mean body temperatures of 20° to 24° C.).

5. It is suggested that the retardation in tumor growth is the result of the combined effects of hypothermia and hypo-oxia. Evidence from the literature is cited to support this view.

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The Determination of Carcinogenic Hydrocarbons in Animal Tissue*

Two-Condition Fluorometry

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(Received for publication July 22, 1943)

While quantitative analyses usually involve at least a partial isolation of the desired substances prior to measurement, many determinations are necessarily made in the presence of extraneous material. In fluorometry partial specificity can be achieved with two filters, one of which transmits wave lengths optimal for exciting the fluorescence of the substance to be measured, and a second filter that corresponds to the wave lengths emitted by that substance. Thus the fluorescence from other materials is either minimized or much of it fails to be recorded. Nevertheless in the analysis of biological materials some extraneous fluorescence almost invariably appears in the final reading. The present study contains a method of correcting for this source of error by means of readings taken either in two properly selected solvents or, better, under two different conditions of oxygenation in the same solvent.

The fluorescence of the carcinogenic and related hydrocarbons has the following properties pertinent to a quantitative determination. It is stable, reproducible, and of sufficient intensity for the accurate measurement of 1 μgm. of hydrocarbon or less (10). It varies directly with concentration (10). It is resistant to alkali (11). It differs significantly from the fluorescence of animal material in such qualities as intensity, spectral distribution, and sensitivity to solvent or to oxygen (11, 12). The fluorescence of the hydrocarbons is strictly additive to the fluorescence of the unsaponifiable matter from animal tissue (11). Inhibitors like oxygen, which alter the fluorescence of the hydrocarbons, do so with such regularity that the result can be calculated from formulas based on the mass law (12).

GENERAL CONSIDERATIONS

The simplest quantitative method for removing the carcinogenic hydrocarbons from treated animal tissue is to saponify the mixture and to extract it with a suitable organic solvent. The unsaponifiable extract then contains all the hydrocarbon present, plus tissue substances, some of which are fluorescent. If the fluorescence of the mixture is then measured in two different solvents, or under two different states of oxygenation, the following considerations obtain:

Let N = Fluorescence ratio for the hydrocarbon; *i.e.*, the ratio of the fluorescent intensities of a unit amount measured under the two experimental conditions employed. Thus, in petroleum ether the fluorescent intensity of benzpyrene happens to be 6.5 times as high in vacuum as in air (12); hence the fluorescence ratio, $N = 6.5{:}1$.

n = Fluorescence ratio for the tissue materials.

R_v = Reading *in vacuo:* the observed fluorescent intensity of the mixture of hydrocarbon and tissue material expressed in arbitrary ammeter units (10).

R_a = Reading in air: the observed fluorescent intensity of the mixture of hydrocarbon and tissue materials. If the readings are taken in two different solvents, R_v and R_a become R_1 and R_2 respectively.

h = Micrograms of hydrocarbon present in the mixture.

K = Micrograms of hydrocarbon per unit of fluorescence in air.

T = That part of R_a due to tissue substances in the mixture.

then

$$R_a = \frac{h}{K} + T$$

$$R_v = \frac{Nh}{K} + nT$$

Solving these equations simultaneously with the elimination of T

$$h = \frac{K(R_v - nR_a)}{(N - n)} \qquad \text{(a)},$$

the basic equation of two-condition fluorometry.

In theory this equation could be applied to the de-

* Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. This investigation was aided by the Wisconsin Alumni Research Foundation and the Jonathan Bowman Cancer Fund.

termination of any material possessing the requisite fluorescent characteristics, but practical considerations limit its usefulness either to a substance not normally present in tissue, or to one that can be removed experimentally by procedures that do not alter the other materials present in the final extracts read routinely. This is due to the fact that the fluorescence ratios, N and n, must be determined separately. While the ratio, N, for the hydrocarbon can be measured accurately on the pure compound, an attempt to determine the ratio, n, for the tissue materials from readings on unknown mixtures would only result in two independent equations containing three unknown terms. In either the two-solvent or the vacuum:air technics the ratio, n, can be determined separately on tissue free of hydrocarbon, and assumed to apply to treated tissue.

The fluorescence of tissue materials is almost the same in the solvents pyridine and petroleum ether (11), and the ratio, $n=1$, can be used routinely when determinations are made with this pair of solvents. In petroleum ether the fluorescence of tissue material *in vacuo* averages about twice that in air. Hence the value $n=2$ can be used routinely in the calculation of results obtained under these two conditions, unless the amount of interfering fluorescence is so large relative to the hydrocarbon that a more exact measurement of the fluorescence ratio, n, becomes desirable; *e.g.*, in liver samples in which the total amount of interfering fluorescence is not only high but variable. The assumption that the value of n obtained from normal tissue holds for tissue treated with hydrocarbon constitutes one of the chief sources of error in the entire determination. Fortunately, however, the magnitude of this error diminishes with a decrease in the total amount of extraneous fluorescence, and when the interference is low n can vary by several hundred per cent without affecting the end result.

A more exact estimation of the value of the fluorescence ratio, n, in treated tissue can be made in the presence of the hydrocarbon if a filter is used that transmits no light below 500 mμ. The fluorescence of tissue material is continuous and of approximately the same intensity at all visible wave lengths, in contrast to the fluorescence from the hydrocarbons, which does not extend above 500 mμ (11). Furthermore, changes in P_{O_2} produce approximately the same relative changes in the intensities of fluorescence at the various wave lengths (12). Determinations *in vacuo* and in air of many samples of mouse tissue indicate that the fluorescence ratios in the range 450 to 500 mμ (Coleman B_2 filter) differ by a factor of 1.06, from those read above 500 mμ (PC-2 filter). Since the B_2 filter is used for measuring the fluorescence of the hydrocarbons, the appropriate fluorescence ratio, n, applicable to this filter equals

$$1.06\ \frac{\text{reading } \textit{in vacuo} \text{ with PC-2 filter}}{\text{reading in air with PC-2 filter}} \qquad \text{.....(b)}$$

For an accurate determination of hydrocarbon in the presence of interfering fluorescence, it is necessary to choose conditions (solvent pairs, or pairs of P_{O_2}'s) in which the fluorescence ratio, N, for the hydrocarbon is large relative to the fluorescence ratio, n, for the tissue substances, and furthermore, the actual fluorescence intensities should be large enough under both conditions to yield reliable readings. The appropriate solvent pairs for the carcinogenic hydrocarbons can be selected from tables determined experimentally (11).

Reagents

1. The carcinogenic hydrocarbon employed in the development of the method was 3,4-benzpyrene. Other hydrocarbons studied included 20-methylcholanthrene; 9,10-dimethyl-1,2-benzanthracene; 1,2,5,6-dibenzanthracene; and anthracene. The purification and fluorescence properties of these hydrocarbons have been described previously (10–12).
2. Petroleum ether. Skelly solve B (b.p. 66–68° C.)
3. Ninety-five per cent ethanol.
4. Distilled water. Water redistilled through block tin proved to be satisfactory.
5. Anhydrous pyridine. Merck reagent.
6. KOH solution. Eighty-five per cent C.P. sticks dissolved in distilled water until 1 cc. = 0.5 gm. KOH. Precipitated carbonate was removed by centrifugation.

All solvents were redistilled through an all-glass still. This procedure yielded a fluorometrically pure solvent as determined with tetranitromethane (11). Contact with rubber, cork, stopcock grease, or any other soluble material was strictly avoided in the various manipulations.

Petroleum ether proved to be excellent both as an extractant and as a medium for the determination of fluorescent intensities. With this solvent tissue materials were extracted from aqueous solution only slowly, whereas microgram quantities of hydrocarbon were removed almost quantitatively in a single extraction.

Apparatus

1. Coleman electronic photofluorometer No. 12, with filters B_2 (400 to 500 mμ.) and PC-2 (500 to 650 mμ). Directions for its use with the hydrocarbons have been given previously (10).
2. Fluorometer tubes.

(a) Ordinary 120 mm. × 18 mm. glass test tubes without lip were satisfactory for readings with different solvents in air. The tubes were selected for size

and marked to give the same reading when filled with a given fluorescent solution (0.0003 per cent quinine sulfate in 1 N H_2SO_4).

(b) For fluorescence readings taken first *in vacuo* and then in air the vacuum fluorometer tube shown in Fig. 1a proved satisfactory. The stopcock and joint were ground with rouge and lubricated with redistilled nonfluorescent glycerol. The tubes were graduated from 8 to 12 cc. in 0.2 divisions.

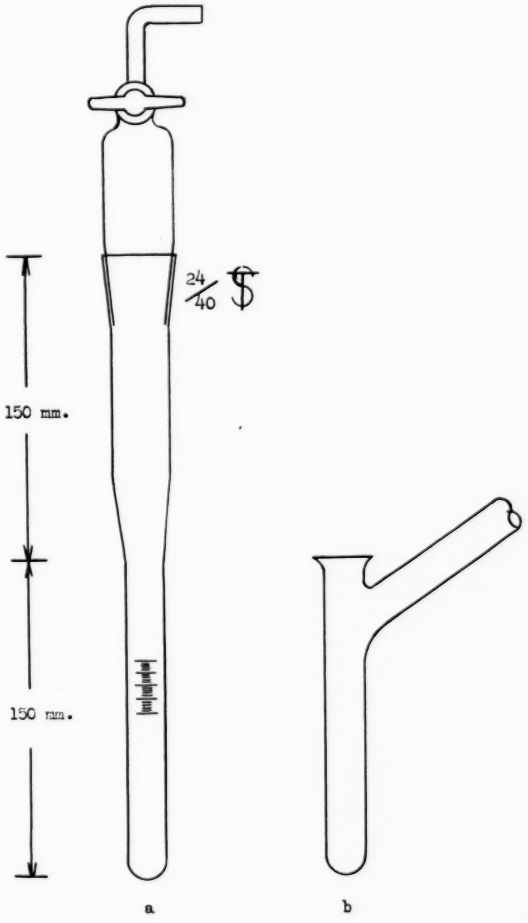

FIG. 1.—Vacuum fluorometer tubes.

(c) Fluorometer tubes with side arms (Fig. 1b). These were used in observing the fluorescence spectra *in vacuo* of extracts containing small amounts of hydrocarbon.

3. Saponification tubes. These tubes were identical with the original plain fluorometer tubes but were kept separate for this purpose.

4. Motor-driven stirrer.

5. Layer separator. The aqueous alkaline layer of saponifiable matter and the layer of petroleum ether containing the unsaponifiable matter were separated from each other quantitatively by means of a special pipet (Fig. 2). Air pressure was used to force the upper layer over into a graduated receiver. The siphon continued a slow delivery unless stopped by raising the receiver high enough to supply an opposing head of solvent. The extract was transferred completely by diluting the remaining layer with pure petroleum ether from the separatory funnel and forcing over the washings several times. The siphon tube was cleaned by washing with pure petroleum ether.

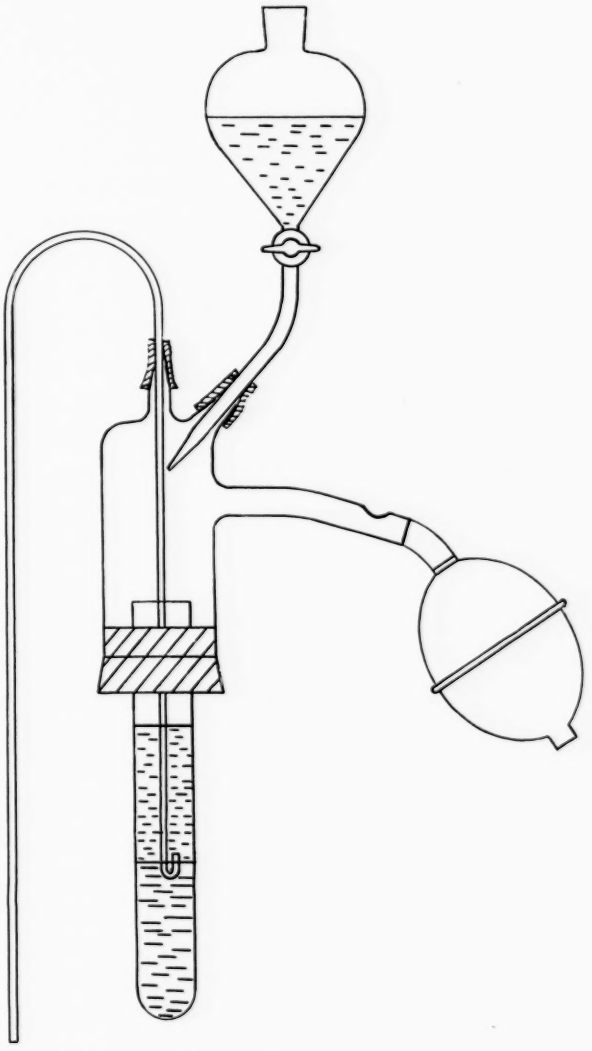

FIG. 2.—Layer separator.

6. Spectroscope. A small Zeiss direct vision hand spectroscope with scale attached was used in the visual observation of the fluorescence spectrum of individual solutions.

PROCEDURE

1. Saponification of tissue.—The tissue was placed cleanly in the bottom of a saponification tube, 4 cc. of 95 per cent ethanol, 1 cc. of the aqueous KOH solution, and a tiny boiling chip were added and the mixture refluxed over steam for $\frac{1}{2}$ to 1 hour under a finger condenser made from a tapered centrifuge

tube. Very fatty tissues required more alkali; saponification was considered complete when the cold mixture contained no oil droplets. Some materials deposited insoluble matter (glycogen from liver, cellulose from feces) but neither the presence of these sediments nor of small bones interfered with the subsequent extraction; when necessary, the liquors were decanted and the residue washed well with pure 95 per cent ethanol. Large organs and carcasses (over 2 gm. fresh weight) were saponified in Erlenmeyer flasks with cold finger condensers. For each gram of fresh tissue 0.5 gm. of solid 85 per cent C.P. KOH and 3 cc. of 95 per cent ethanol were employed.

2. *Extraction of nonsaponifiable matter.*—After completion of the hydrolysis the tubes were cooled at the tap and made up to about 10 cc. with distilled water, and 10 cc. of petroleum ether added. The mixture was stirred vigorously by a motor for 5 minutes and the layers then allowed to separate for 5 to 10 minutes more. Under these conditions one extraction was sufficient to remove 95 to 100 per cent of small amounts of hydrocarbon (1.0 μgm. or less). For larger amounts of hydrocarbon the saponification mixture was made to volume with ethanol, an aliquot diluted to 50 per cent alcohol and extracted as above.

If the amounts of tissue were large and only a small amount of hydrocarbon was present, the whole saponification mixture was diluted to 50 per cent alcohol and extracted by stirring for 10 minutes with 3 successive portions of 25 to 50 cc. of petroleum ether. The layers of petroleum ether were removed in a separatory funnel, free of grease, taken to dryness *in vacuo* at 60° C. in an all-glass still, and the residue made up to volume with petroleum ether.

3. *Measurement of fluorescence.*—A suitable aliquot of each extract was placed in a vacuum fluorometer tube and petroleum ether was added to a volume of about 13 cc. The tube was then evacuated with continuous shaking at room temperature until the volume was approximately 10 cc., when only solvent vapor remained above the solution. Any dried material splattered on the side was brought into solution by cautiously inclining the tube. The volume was read accurately, and the tube placed in the fluorometer for the measurement of the fluorescence with the B_2 filter (450 mμ±). When a very accurate determination of extraneous fluorescence was necessary, the fluorescence of the mixture was read also through the PC-2 filter. The readings of the fluorescent intensities *in vacuo* remained constant even after agitating the solution unless leaks were present, in which case a gradual decrease in the readings resulted.

For the reading in air, the stopcock was opened and the system equilibrated by hitting the end of the tube against the palm of the hand. The volume of the solution was read accurately, usually 0.1 to 0.2 cc. higher than the volume *in vacuo,* and the fluorescent intensity read in the fluorometer with the B_2 filter. If the extraneous fluorescence was known to be large, a reading was also taken with the PC-2 filter. For convenience in calculation, all readings were corrected to a volume of 10 cc. The appropriate numerical values were then substituted in formula (a): $N=6.5$ for benzpyrene, and $n=2$. For special tissues the value for n was obtained from the readings with the two filters in equation (b). Data for values of N for other hydrocarbons are available in tables (12).

In an alternate procedure two identical aliquots of the original petroleum ether extract are taken to dryness *in vacuo,* and then made up to 10 cc. with pyridine and petroleum ether. The fluorescent intensities in the two solvents are sufficiently different for equation (a) to be usable: $N=3.8$ for benzpyrene (11) and $n=1$.

Recovery Experiments

The assumptions implicit in the derivation of equation (a) as well as the practical utility of the method were evaluated by means of recovery experiments carried out with mixtures of pure hydrocarbons or with mixtures of hydrocarbons and animal tissue. The fluorescence ratio for anthracene (12) from vacuum to air equals 1.6:1 and this figure is approximately equal to the corresponding ratio for unsaponifiable matter from tissue. Analyses of mixtures of benzpyrene and anthracene were therefore made as an index of the degree of accuracy to be expected in the determination of benzpyrene in tissue when the ratio, n, of the tissue interference (anthracene) is known with certainty. The results (Table I) reveal errors of only 2 per cent for amounts of benzpyrene of 0.1 μgm or more. Errors of 10 per cent were encountered with 0.05 μgm. of benzpyrene, which was considered the lower limit of the method. When either component accounted for only a small fraction of the total fluorescence, the error in its determination was comparatively large.

In Table II data are given for the recovery of 1 μgm. of benzpyrene added to various mouse tissues and to entire mouse carcasses. The errors observed in most determinations were considerably less than 10 per cent, and the average error in any series of materials never exceeded 4 per cent. The positive and negative distribution of errors was approximately the same, indicating that for all practical purposes the single extraction employed sufficed for the removal of this quantity of hydrocarbon.

A very extensive series of recovery experiments was also carried out with the two-solvent technic involving the use of petroleum ether and pyridine for

the final readings. Average errors of ±4 per cent were observed when 1.0 μgm. of benzpyrene was present per mouse carcass. With smaller amounts of hydrocarbon the percentage error increased although reasonable recoveries were observed with some tissues, *e.g.* spleen, for as little as 0.02 μgm. of benzpyrene (9). Nevertheless, the vacuum:air technic was preferred over the two-solvent method because it involves fewer manipulations, because the distribution of errors was somewhat better, and because a more accurate evaluation of the ratio, *n*, is possible.

Recovery experiments with hydrocarbons other than benzpyrene revealed that the method is applicable to the following amounts of carcinogens: 0.5 μgm. of methylcholanthrene; 0.5 μgm. of 9,10-dimethyl-1,2-benzanthracene; and 10 μgm. of 1,2,5,6-dibenzanthracene.

Errors and Limits of Method

The errors in the fluorometer readings themselves were due chiefly to line fluctuations in the instrument and to manipulative errors in the preparation of the sample. The chief remaining error was the uncertainty in the value of the fluorescence ratio, *n*, for the interfering substances in the sample. Further limits were placed on the method by the relative amounts of hydrocarbon and interfering agents present. The expected error in the calculated amount of hydrocar-

Table I: Analysis of Mixtures of Benzpyrene and Anthracene
Vacuum:Air Technic

Added benzpyrene, μgm.	Added anthracene, μgm.	Fluorescent intensities in 10 cc. petroleum ether *		Recovered benzpyrene, μgm.	Error, per cent	Recovered anthracene, μgm.	Error, per cent
		In air,† ammeter units	In vacuum, ammeter units				
0.2	1.0	17.0	77.0	0.203	+ 1.5	0.87	— 13.0
0.2	2.0	26.0	90.0	0.196	— 2.0	2.05	+ 2.5
0.1	3.0	28.0	70.5	0.102	+ 2.0	2.91	— 3.0
0.1	5.0	44.0	96.5	0.102	+ 2.0	4.93	— 1.8
0.05	5.0	42.0	79.0	0.045	— 10.0	5.05	+ 1.0
0.05	7.0	57.5	106.0	0.053	+ 6.0	6.95	— 0.7

* Scale set so that 50 ammeter units ≃ 0.1 μgm. benzpyrene per cc. petroleum ether in air.
† Average atmospheric pressure = 740 mm. of Hg.

Table II: Recovery of Added Benzpyrene from Mouse Tissue
Vacuum:Air Technic

Tissue	Number of determinations	Average wet weight, gm.	Added benzpyrene, μgm.	Fluorescent intensities of ½ aliquot in 10 cc.*		Average *n*	Average recovered benzpyrene, μgm.	Error	
				In air,† ammeter units	In vacuum, ammeter units			Average, per cent	Range, per cent
None (reagent blank)	11	...	..	0.15	0.28	....	0.0019	+0.19 ‡	+ 0.14 to + 0.6 ‡
None (hydrocarbon recovery)	8	...	1.0	12.7	80.8	....	0.991	—0.9	— 4.7 to + 6.1
Liver	12	0.79	1.0	17.5	90.1	2.04:1	0.967	—3.3	— 6.2 to + 8.0
Lungs	8	0.20	1.0	12.6	81.9	2.02:1	1.004	+0.4	— 3.2 to + 7.8
Organs (kidneys, spleen, heart)	8	0.74	1.0	12.4	81.1	2.0:1 §	1.001	+0.1	— 3.1 to + 6.3
Fat	8	1.04	1.0	12.3	82.6	2.0:1 §	1.032	+3.2	— 6.4 to +13.5
Intestine (washed)	12	1.26	1.0	13.1	84.2	2.0:1 §	1.030	+3.0	— 5.7 to +10.8
Brain	4	0.84	1.0	12.3	81.1	2.0:1 §	1.003	+0.3	— 1.6 to + 1.6
Carcass (whole–minus above tissue)	8	14.80	1.0	15.6	58.7	2.04:1	0.960	—4.0	—12.0 to +12.0

* Scale set so that 50 ammeter units ≃ 0.1 μgm. benzpyrene per cc. petroleum ether in air.
† Average atmospheric pressure = 740 mm. of Hg.
‡ Based on 1 μgm. benzpyrene.
§ With these tissues the amount of interference was too low (0 to 1 ammeter units) for direct determination of *n*, and the value 2 was used in the calculations.

bon present was arrived at in the following manner (5):

Let $\triangle n$, $\triangle R_a$, and $\triangle R_v$ be the errors in the respective measurements n, R_a, and R_v. Since N and K are determined on the pure hydrocarbon these values may be considered accurate. By differentiation the separate errors in h, due to individual errors in n, R_a, and R_v are

$$\Delta h_n = \frac{-KT}{(N-n)}\Delta n$$

$$\Delta h_{R_a} = \frac{-nK}{(N-n)}\Delta R_a$$

$$\Delta h_{R_v} = \frac{K}{(N-n)}\Delta R_v$$

The combined error in h is

$$\Delta h = \frac{K}{(N-n)}\sqrt{(T\Delta n)^2 + (n\Delta R_a)^2 + \Delta R_v{}^2}$$

As an illustration of the use of this equation, assume the following errors in a typical determination of benzpyrene in mouse tissue with petroleum ether as the solvent wherein $n=2$, $N=6.5$, $K=0.02$ μgm. per ammeter division: $\triangle n = \pm 0.2$, $\triangle R_a = \triangle R_v = \pm 2$ of the 100 ammeter divisions of the scale. When the tissue interference, T, amounts to 5, the error in h is ± 0.02 μgm. benzpyrene. In the vacuum:air technic 0.3 μgm. of benzpyrene per 10 cc. is about the largest amount of hydrocarbon that can be measured with the Coleman fluorometer. Thus the expected error would be approximately ± 7 per cent. Actually, the observed average error was less than ± 4 per cent (Table II).

The construction of the fluorometer was such that an important limiting factor in the sensitivity of the method was the density of the transmitting filter used. The intensity of the recorded fluorescence per unit of hydrocarbon could, of course, be increased by the use of a less dense filter transmitting in the same range. However, the recorded tissue interference would also be increased correspondingly and the net result, therefore, would not be an increase in the sensitivity of the method. For extracts nearly free of interference, however, the elimination of the second filter might prove to be of advantage. When a more transparent filter was used to absorb only the scattered ultraviolet light, it was possible to adjust the instrument so that 1 ammeter unit was equivalent to only 1 millimicrogram of benzpyrene in 10 cc. of petroleum ether *in vacuo,* instead of the usual value of 3.08 millimicrograms per division with the denser filter. In other words, a threefold increase in sensitivity was achieved. Still another means of increasing the sensitivity of the method could be to compare readings *in vacuo* with those in pure O_2 rather than in air. This variation, like the change in filters, would be most effective for solutions relatively free of extraneous fluorescence.

In the determination of hydrocarbons in treated tissue, a very serious error would result if metabolic derivatives of the hydrocarbon were present with fluorescent characteristics similar to those of the hydrocarbons themselves. The petroleum ether extracts as read routinely would be expected to contain neutral products such as alcoholic, ketonic, or quinoid derivatives of the hydrocarbons. Basic derivatives of the hydrocarbons have not been reported, and if they did exist, they would presumably contain nitrogen in a linkage that would reduce the solubility of the compound in petroleum ether. Acidic, enolic, and phenolic (2–4) derivatives would be retained by the strongly alkaline solution from which the petroleum ether extract is made. This was demonstrated with several fluorescent phenols.[1] Ten micrograms each of 3-hydroxypyrene; 4-hydroxypyrene; 5-hydroxypyrene; and the rat and mouse metabolite, 4′,8′-dihydroxy-1,2,5,6-dibenzanthracene were separately dissolved in 50 per cent ethanol-KOH solution, refluxed for $\frac{1}{2}$ hour, extracted with petroleum ether, and the fluorescence measured. About 0.3 to 1.0 per cent of the phenols were extracted from the aqueous alkaline phases, and in no case was the resulting fluorescence equivalent to more than 0.01 μgm. of benzpyrene per cc. The 5,8- and 5,10-quinones of 3,4-benzpyrene, on the other hand, were included in the unsaponifiable extracts, but these derivatives proved to be only very weakly fluorescent.

Most of the spectra of the carcinogenic hydrocarbons are banded in the region 400 to 500 mμ, and are easily observed in microgram quantities with a direct vision hand spectroscope. If a foreign spectrum is present, the calculated values for the amount of hydrocarbon present must be viewed with caution.

Other Methods

While the present method was being developed an alternate procedure was described by Berenblum and Schoental (1) "for the quantitative estimation of 3,4-benzpyrene in whole mice, separate tissues and excreta, based on the 'wet' method of extraction and spectographic analysis of the fluorescence. . . . The limit of sensitivity . . . was found to be in the region of 0.05 μg./mouse, while the accuracy was of the order of ± 20 per cent over a range of 1-10,000 μg/mouse." Their procedure involved: (a) saponification, (b) extraction with benzene after acidification, (c) formation of emulsions with the benzene extract and aqueous sodium carbonate to remove impurities, (d) separation of the emulsion by centrifugation, (e) purification by adsorption on a column of alumina, and (f) estimation of the hydrocarbon in the final

[1] Kindly supplied by Dr. R. Norman Jones, of the Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts; now of Queen's University, Toronto.

benzene extract by visual comparison of a photograph of its fluorescence spectrum with similar spectra of known amounts of benzpyrene. The spectrographic technic employed was not described in detail, nor was a statement made of the time of exposure to ultraviolet light in photographing. The latter factor could seriously affect the accuracy of the method since the fluorescence of these hydrocarbons, and of benzpyrene in particular, is diminished on prolonged exposure to ultraviolet light (11). It would appear therefore that the two-condition technic is to be preferred over the photographic method as both simpler and more accurate.

The spectrographic method for the determination of the carcinogenic hydrocarbons has probably been studied more extensively than any other (6-8), and in the presence of animal material the lower limit of this method appears to be about 10 μgm. of dibenzanthracene. The absorption of ultraviolet light by the other carcinogenic hydrocarbons is less intense, with a corresponding decrease in the sensitivity of the method. It is of interest that investigators who use the spectrophotometric method employ dibenzanthracene as the hydrocarbon of choice, whereas those using fluorometric methods employ benzpyrene. Dibenzanthracene happens to have a particularly intense absorption spectrum, and a relatively weak fluorescence. Benzpyrene, on the contrary, has an unusually intense fluorescence spectrum. On the basis of reported sensitivities it would appear that for the determination of anthracene the spectrophotometric method is to be preferred (6); for dibenzanthracene the spectrophotometric and the fluorometric methods are of approximately equal value; while for the potent carcinogens, 9,10-dimethyl-1,2-benzanthracene, methylcholanthrene, and benzpyrene, the fluorometric method is many times more sensitive than the spectrophotometric one.

SUMMARY

A system of two-condition fluorometric analysis was devised and applied to the determination of the carcinogenic hydrocarbons in animal tissue. The hydrocarbon was separated from the treated tissue in the unsaponifiable fraction, the majority of the tissue fluorescence eliminated by selected filters, and the remaining interference eliminated by calculations based on readings taken either in two selected solvents or under two different partial pressures of oxygen in the same solvent. By either technic it was possible to recover 1 μgm. or less of benzpyrene added to mouse tissue with average errors of ± 2 to 5 per cent. The lower limit of the method appeared to be about 0.05 μgm. of benzpyrene.

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A Sarcoma-Producing Factor Extractable from Transplanted Rat Fibrosarcomas*

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(Received for publication May 29, 1943)

A number of investigators (Schabad, Menke, Kleinenburg, and Steiner) have reported the extraction of fat-soluble tumor-producing substances from human tumors and also from the liver of human beings afflicted with neoplasms. The injection of the extracted fatty compound into mice and rats, however, produced tumors in only a small percentage of the treated animals.

There were available a number of rat spindle cell and mixed cell sarcomas that had been induced by one of the carcinogenic hydrocarbons in the inbred albino rats of Dr. King's colony. These tumors had been transplanted through 20 to 40 passages, and had proved to be 100 per cent transplantable in rats of this strain. It seemed worth while to attempt to extract a tumor-producing factor from the transplanted rat sarcomas, for if such a factor could be obtained it might produce more tumors when injected into rats of the strain in which the tumors originated than had been obtained by other investigators in the animals injected with human material.

METHOD

Rat sarcomas that had grown in every one of the rats in the 20 to 40 passages through which they had been transplanted were excised from etherized rats. The tumors were ground into small particles, mixed with an equal volume of 95 per cent alcohol, and allowed to stand in the refrigerator at 4° C. overnight. The tissue was then pressed through a gauze filter, ground into smaller particles, and pressed between sheets of absorbent paper to remove the excess fluid. After this partial drying the tissue was placed in 2 volumes of benzol [1] in a flask to which was attached an extraction apparatus and extracted in an incubator at 42–45° C. for 8 hours on 3 successive days. After this the extract was filtered off and concentrated *in vacuo* at 42–45° C.

The fat obtained in this manner was slightly tan colored, resembling vaseline. It was soft at room temperature, but became sufficiently fluid for injection when kept for a few minutes at 44–46° C.

Twenty-eight inbred albino rats 21 to 40 days old were injected with the fat extracted from the rat sarcomas. Some rats received 0.12 cc. while others received 0.25 to 0.5 cc. About 4 months later these rats received into the same site 0.5 cc. of fat extracted in the same manner. During the following 6 months 5 of the rats developed tumors at the injection site. Three of them were transplanted and proved to be fibrosarcomas transplantable through many passages in rats of their strain of origin. The negative rats were kept for 10 months after the second injection. They were then autopsied. Two of them had tiny spots in their lungs. These were not considered sarcomas as they did not grow when transplanted into susceptible rats.

An attempt was also made to extract by means of benzol a tumor-producing substance from livers of rats bearing transplanted rat sarcomas. Twenty-four rats of the inbred albino strain 28 to 40 days old were injected with 0.12 to 0.5 cc. of fat extracted from livers. Four months later they received a second injection consisting of 0.5 cc. of a similar extract. Two of the rats developed sarcomas at the site of injection, one 4 months and the other 5 months after the second injection. One of the tumors was transplanted through 6 passages in rats of its strain of origin.

One female rat of the first group injected with fat from sarcomas, and one female rat of the second group injected with fat from liver, developed tumors in the mammary gland in the region that had been injected 9 months earlier.

Microscopical preparations of the tumors that arose following injection of the extracted fat showed that 7 of them were spindle cell sarcomas, 1 was a mammary gland adenoma, and 1 a colloid carcinoma.

In previous work with inbred rats of Dr. King's colony it was noted that they developed fewer neoplasms than rats of other strains. However, in order

* This investigation was aided by a grant made to Dr. Warren H. Lewis from The International Cancer Research Foundation.

[1] Reagent benzene (Merck) thiophene-free.

to ascertain the number of spontaneous tumors that arose in rats of the inbred albino strain during the course of this study 200 rats were autopsied when 10 to 12 months old. Every one of them proved to be free from neoplasms (sarcoma, lung tumor, adenoma, and lymphosarcoma). Therefore, we are led to conclude that none of the sarcomas that developed following injection of extracted fat were of spontaneous origin. On the other hand the 2 epithelial tumors may have been spontaneous growths whose development was hastened by the presence of the injected fat, since the majority of tumors induced by carcinogenic agents have proved to be sarcomas.

In studies on the susceptibility of rats of the inbred albino strain to the development of induced tumors, 120 rats were injected with one of the carcinogenic agents (dibenzanthracene, benzpyrene, or methylcholanthrene) and every one of them developed a sarcoma at the injection site.

The percentage of tumors induced in rats of the inbred albino strain by the injection of fat extracted from rat tumors and from the livers of tumor-bearing rats was slightly larger than that obtained by some of the previous investigators by means of fat extracted from human material; however, it was still small in relation to the number of rats treated.

CONCLUSIONS

Attempts were made to extract by means of benzol a tumor-producing factor from transplanted spindle cell and mixed cell rat sarcomas and from the liver of rats bearing this type of sarcoma.

The extracted fat was injected into young rats of the inbred albino strain. Rats of this strain had proved to be 100 per cent susceptible to the growth of grafts of the tumors used for extraction.

Sarcomas developed at the injection site in 5 of the 28 rats injected with the fat extracted from the tumors and in 2 of the 24 rats injected with the fat extracted from the liver.

In addition to the 7 sarcomas 1 adenoma developed at the site of injection of the fat extracted from the sarcoma and 1 carcinoma arose at the site of injection of the fat extracted from the liver.

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Estrogen Administration to Aged Female Monkeys with No Resultant Tumors*

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(Received for publication July 7, 1943)

The carcinogenic effects of estrogens in many strains of mice and some rats are well known, but there has been no successful attempt to produce tumors in monkeys by estrogen administration. The present report describes such an experiment.

Reports of spontaneous malignant tumors are rare in subhuman primates. One instance of an adenocarcinoma of the prostate in an old monkey was reported previously (Engle and Stout). In this report, reference is made to the neoplasms in lower primates already recorded in the literature, and to the observations of Ratcliffe who described a fibroadenoma of the uterus in a baboon and a papilloma of the cervix in a macaque. There has been no instance reported of an adenocarcinoma of the mammary gland or of the corpus uteri in the primates.

As Engle and Stout have indicated, the life span of primates in captivity is in general considerably less than may be expected of similar animals in the wild state, so that such animals in close captivity do not live to an age when spontaneous tumors might be expected to appear.

Thus, as has been said, reports of spontaneous tumors in monkeys are very rare, and there is no instance of an induced malignant tumor in subhuman primates.

Hartman, Geschickter, and Speert treated animals over a period of months with various estrogens and no neoplasm has, as yet, resulted. But these animals were young, or young mature females, and even though an estrogen might be carcinogenic in rhesus monkeys the period of treatment required may be very long.

The present report concerns treatment of 5 old female rhesus monkeys (*Macaca mullata*) with α-estradiol for more than 2 years. One of these animals died of intercurrent complications.

A free-ranging colony of rhesus monkeys was established in Santiago Island, adjacent to Puerto Rico, in 1938, under the auspices of Columbia University and the School of Tropical Medicine of the University of Puerto Rico.

The monkeys were selected in India by Dr. C. R. Carpenter. Healthy animals of diverse ages were secured and liberated on a 35 acre island. From this group, 5 old females and 5 old males were later selected and removed from the free-ranging colony to quarters at the School of Tropical Medicine in San Juan. The animals were kept in large outdoor runs, which communicate with smaller but commodious quarters for sleep and shelter. The health and condition of the animals in these cages was excellent.

After some months of observation, estrogen treatment was instituted in the 5 females in July, 1940. In June, 1942, owing to restricted conditions arising out of the war, the animals were brought to the New York laboratory, where they were watched, but no further treatment was given.

These 5 old female rhesus monkeys were selected because of physical indications of old age. The flabby breasts and flaccid perineums were indications of previous pregnancies. Menstrual cycles were not observed, but such phenomena could have been missed, and because the animals were not handled daily negative observations have little value. It is not known if female monkeys have a menopause. The maximum life span of rhesus monkeys is not known, either in a wild or captive state. Any suggestion of the ages of these experimental monkeys would be speculation. Guesses, based on development and puberty, might suggest that few monkeys even under optimal conditions would reach the age of 20 years, and that these animals were some years younger than this, but compared to other females of the colony these were aged.

EXPERIMENTAL

These animals were treated with implantations of crystals or pellets of α-estradiol. Implantations were

* Aided by a grant from The Rockefeller Foundation, administered by Dr. P. E. Smith.

The Santiago Primate Colony was founded with a grant from the John and Mary Markle Fund.

The α-estradiol used in these studies was generously supplied by the Ciba Pharmaceutical Products, Inc., through the courtesy of Mr. R. C. Mautner.

A portion of this work was aided by a grant from the Josiah Macy Jr. Foundation.

Aided by a grant from Liggett and Watters Fund for Cancer Research, of the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York, N. Y.

made at approximately 5 to 6 week intervals. The details of treatment are given in Table I. For the first few months, crystals of the estrogen were used. The skin and superficial fascia at the edge of the mammary gland were reflected, and after careful drying of the exposed surface the crystals were dusted onto the under surface of the mammary gland and onto the deep pectoral fascia. It is known that estrogens have an intensified local action greater than the general systemic effect. Treatments with crystals were administered from July or August to January.

After this period, treatment of the breast locally was discontinued. Some scarring occurred, and continued treatment might reduce the vascular supply to the gland. Biopsies were made of the mammary glands of 2 animals when the breast as implantation site was abandoned.

Pellets of crystals, implanted into the thigh, were used for 10 months, after which crystals implanted into the thigh were used for the remainder of the treatment period. The total dosage for each of the 4 animals was 825, 600, 575, and 785 mgm. of α-estradiol (Table II). The pellets were not as satisfactory as the crystals. In several instances they were walled off, and no change in size could be determined by manual examination. Too frequently ulceration of the site with extrusion and loss of the pellet occurred. The animals, therefore, received less than the stated dosage of estrogen.

Complete autopsies were made on 3 monkeys, the other (No. 777) having died during the night, and a

TABLE I: TREATMENT OF MONKEYS BY IMPLANTS OF α-ESTRADIOL

	α-Estradiol implantation			
Monkey	Date, 1940	Interval, days	Site	Media
777 *	July 10		R.M.G.	Crystals, 50 mgm.
778				
779 *				
778	Aug. 7	27	"	" " "
780	" 7		"	" " "
	Sept. 18	41	"	" " "
	Oct. 30	41	"	" " "
	Dec. 12	42	"	" " "
	1941			
	Jan. 22	40	"	" " "†
	Feb. 20	29	Thigh	Pellet, 50 mgm.
		Months		
777 *	Mar. 6	8	"	" " "
779 *	" 6	8	"	" " "
		Days		
777	Apr. 4	29	"	" " "
778	" 4	42	"	" " "
779	" 4	29	"	" " "
780	" 4	42	"	" " "
	May 21	46	"	" " "‡
	July 2	41	"	" " "
	Aug. 13	41	"	" " "
	Sept. 24	40	"	" " "
	Nov. 13	49	"	" " "
	Dec. 31	47	"	Crystals, 50 mgm.
	1942			
	Feb. 13	44	"	"
	Mar. 31	46	"	"
	May 15	42	"	"

Arrived at New York, June 19, 1942.

* Animals 777 and 779 received estrogen implants on July 10, 1940, and no further treatment until Mar. 6, 1941. Thereafter treatments were continuous.

† No. 780 received 35 mgm.

‡ Nos. 778, 779 received 25 mgm.

TABLE II: SUMMARY OF TREATMENT

	Autopsy				
Monkey	Date, 1942	Weight, gm.	After last implant, months	Treatment, months	Total, mgm.
778	July 16	5,440	2	24	825
777	Aug. 3	3,950	3	25 (16)	600
779	Nov. 4	3,610	6	28 (20)	575
780	Nov. 10	4,850	6	27	785

* First figures represent elapsed time from first treatment to autopsy. Figures in parentheses are months of consecutive treatment.

limited number of organs were studied. Microscopic examination for the other animals was made of the following organs: liver, spleen, lung, both kidneys, thyroid, thymus, adrenals, hypophysis, heart and coronary arteries, thoracic and abdominal aorta, superior cervical ganglion, cervical spinal cord and spinal ganglia, selected tissues from gastrointestinal tract, and an especially detailed examination of the genital tract and mammary glands was carried out.[1]

Aside from incidental lesions of the intestine, these animals present little of interest except for the mammary glands and the genital tract. The report on these organs is therefore presented in some detail.

MICROSCOPIC FINDINGS

Ovaries.—Ovaries of monkeys 778 and 779 are available for study. Monkeys 777 and 780 had been ovariectomized shortly before treatment was begun. The morphology of the ovaries of the 2 animals is similar.

The germinal epithelium is intact and of normal low columnar appearance. The tunica albuginea is heavy and fibrous, with no epithelial pockets indicative of new formation of ova or follicular cells. The cortex has a large number of primitive ova and primordial follicles. Many of these primordial follicles located in the deeper levels of the cortex have undergone atresia. There are no corpora lutea, either recent or old, in these ovaries. A few medium sized follicles, all in various stages of degeneration, are distributed through the ovary. The most constant structures in the ovary are the heavily scarred remnants of atretic follicles. Undoubtedly follicular growth has been proceeding to the stage of a medium sized follicle. Atresia has then ensued with the resulting corpus albicans of atresia. These structures are more pronounced and more numerous than usually seen in human ovaries. Structurally, these ovaries are very similar to the ovaries of monkeys that have received treatment with gonadotropic hormone from the urine of pregnancy (Engle, 1933). Many of these fibrous bodies contain the ghosts of entrapped ova that have degenerated.

Mammary glands.—The mammary glands in the female monkey, in their inactive or nonlactating phase, are made up of large gland fields closely packed together (Fig. 1). The stroma is dense and does not contain as much fat as in the human breast. The ducts in the monkey are relatively small and are lined by a single layer of cuboidal epithelium. We have not seen in the mammary ducts of the untreated monkey any of the varied proliferative epithelial changes that are so common in the ducts of the human breast.

In 2 of the 4 monkeys treated with α-estradiol (Nos. 779 and 780) definite cystic change was seen in the mammary glands. It consisted in dilatation of the ducts to many times their normal size (Fig. 2). They contained epithelial debris and leukocytes. The lining epithelium was quite normal, however, and showed no papillary or any other kind of proliferation. The gland fields appeared to be entirely normal, and failed to show any proliferation of the acinar epithelium.

The mammary glands in the other 2 monkeys showed nothing abnormal.

Uterus, cervix, and vagina.—The uterus of monkey 777 is of normal size. The musculature is normal in position and quantity. The vessels are badly sclerosed. The entrance of the uterine tube into the myometrium shows loss of circular muscle layer, which is replaced by a thick layer of collagenous tissue. The epithelium of this portion of the tube is low columnar in inactive stage.

The endometrium is greatly reduced in thickness. There is evidence of atrophy in the sparse glands, with a thick, densely packed stroma and pyknotic nuclei of stromal cells. A few areas of cystic glandular hyperplasia are noted. No necrosis is present but some areas show leukocytic infiltration.

The cervix shows extensive squamous cell metaplasia throughout the cervical canal, these cells replacing much of the columnar surface of the glands. Some pearl formation is seen in the acini of the glands. Little leukocytic infiltration has occurred.

The epithelium of the vagina is normal, comparatively thin, with the outer half keratinized. Some epithelial dehiscence into the lumen occurs.

[1] Monkey 113 had received a total of 735 mgm. before June, 1942, when it developed paralysis of both legs. This condition slowly progressed until it finally died, about 10 days after the onset. The following were the pertinent gross autopsy findings: Crown–rump length, 47 cm., and from great trochanter to toes 44 cm.; sacral decubitus ulcer, cysticercus lesions of lung and liver; paralytic distended urinary bladder with hemorrhagic cystitis; large soft uterus with thick homogeneous myometrium and very thick endometrium, the latter presenting whitish or yellowish streaks with some vertical ellipsoidal cysts. *Vagina:* Thick, wrinkled, frosted, white mucous membrane with fecal soiling. *Ovaries:* Small, smooth, with no identifiable mature follicles or corpora lutea. *Fallopian tubes:* Normal. Extensive myelomalacia of the spinal cord.

Emulsions of brain and cord were inoculated intracerebrally into mice and serially passaged but no virus disease could be established.

Microscopic findings confirmed the extensive myelomalacia of the posterolateral columns of the spinal cord and bronchopneumonia as the main contributory factors in the death of the animal. The findings in the genital tract and mammary glands were essentially the same as in the other 4 monkeys, *viz:* Hyperplastic cystic endometrium, squamous epithelial metaplasia of the endocervix and hyperkeratinization of the vagina; many ova in the ovary, few developing follicles, many atretic follicles, no corpora lutea; in the mammary glands some dilatation of the main ducts with inspissated hyaline contents both here and in the smaller radicles.

Smooth muscle is apparently reduced and the stroma is heavily fibrous.

The uterus of monkey 778 is of normal size. The myometrium shows a normal musculature. The blood vessels of the myometrium show extensive sclerosis. The arteries also show loss of muscle and increase of collagenous fibers in the media. The intima shows extensive lamination, fibers reacting to elastic tissue stain are disorganized and have lost their characteristic appearance.

At the apex of the fundus there is a subserous cyst, 3 mm. in diameter. This is an isolated cyst, which pits the musculature of the fundus and protrudes above the surface covered by a very thin layer of connective tissue and by the peritoneum. It is lined by a single layer of low epithelium and filled with a mucus-like secretion. Its origin is unknown, but it is similar to cysts occurring near either gonad, which are known to be embryonic rests.

FIG. 1.—Mammary gland of normal adult female monkey.

The endometrium has generalized cystic glandular

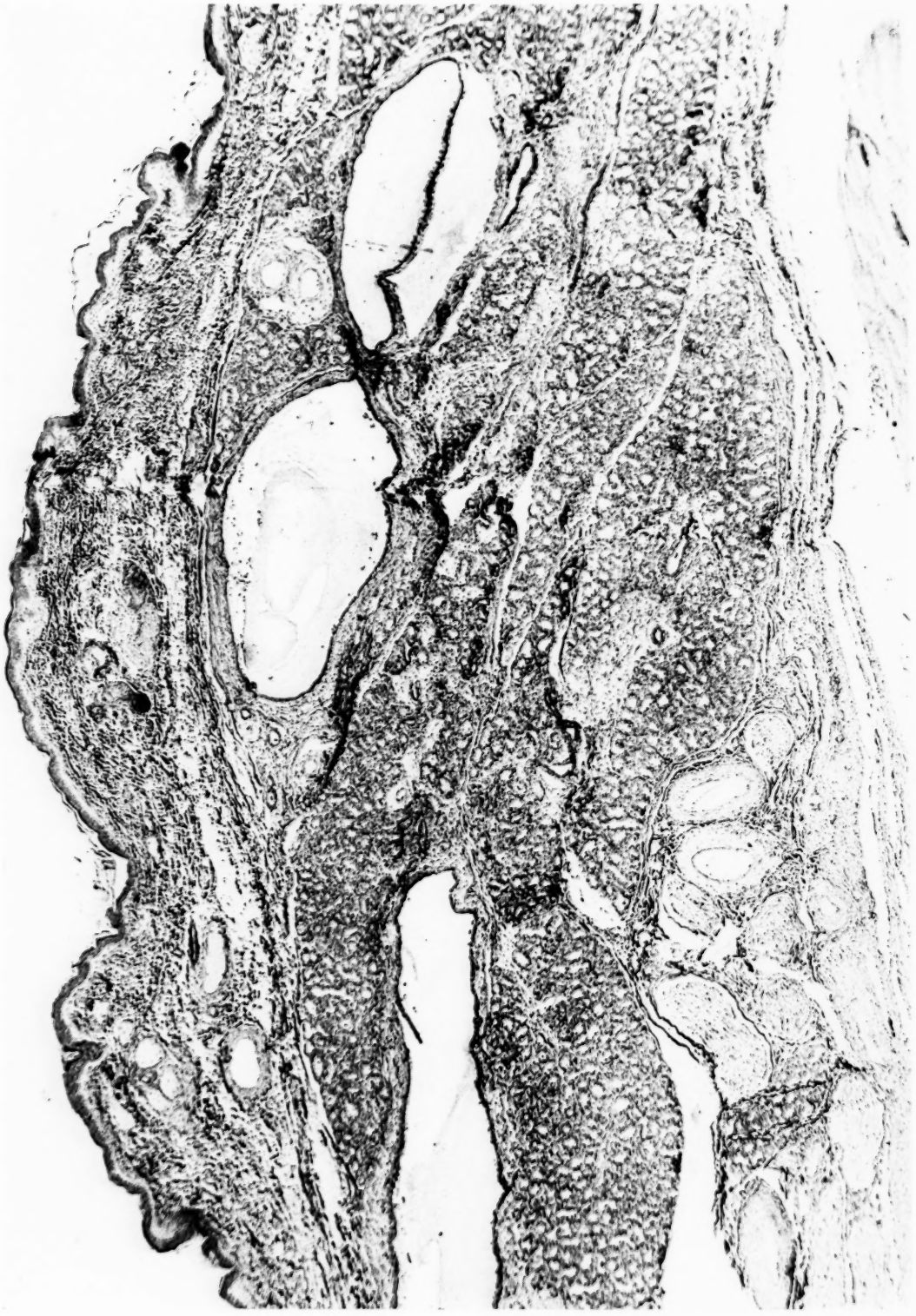

FIG. 2.—Mammary gland of estrogen-treated monkey 780, showing dilated ducts.

hyperplasia with endometritis. The endomentrium is reduced in volume and thickness, and the lumen is difficult to recognize. In many glands the epithelium is tall and in active secretion. In the larger cystically dilated glands, which are distended with fluid, the epithelium is reduced to a low cuboidal type and appears to be inactive in secretion.

The stroma shows heavy infiltration of leukocytes, which also appear in the lumens of the cystic glands. The inflammation extends into the muscle below the basalis, obscuring the identity of the latter zone.

The cervix has extensive squamous cell metaplasia into the endocervix and the racemose glands. Little secretory epithelium remains and the cervical canal is free of mucus. Considerable endocervicitis is present, with leukocytes penetrating the metaplastic squamous epithelium.

The vagina shows a very thick mucosa, with the surface portion heavily keratinized and a large amount of epithelial desquamation. The muscle is apparently reduced and the elastic tissue sparse. Heavy fibrous masses form the walls of the vagina.

The uterus of monkey 779 is of average size. Preparations made with Masson's trichrome stain indicate a large amount of collagenous fibers in relation to the smooth muscles. The blood vessels are somewhat sclerosed, with extensive thickening of the intima.

The endometrium has cystic glandular hyperplasia without endometritis. The lumen of the uterus is not occluded. The cystic glands are large, containing some secretion, but with no desquamated cells or white blood cells. The epithelium of the glands is of the high columnar estrogenic type. The basalis is slightly changed and with normal glands. The stroma of the basalis is very dense with packed, pyknotic connective tissue cells.

The cervical canal shows extensive, if not complete, keratinization of stratified squamous epithelium, with much dehiscence of this epithelium into the canal. There is little mucus in the racemose glands. The columnar cells of these glands are high, with many vacuoles in the cells. In many acini several layers of squamous cells have pushed the columnar cells toward the lumen, although the latter are entirely intact as a covering mucosa. Epithelial pearls are abundant.

The vagina is not excessively thick, having about 20 cell layers, the outer one-third of which are keratinized. There is a moderate amount of desquamation into the lumen.

The uterus of monkey 780 is larger than any nongravid uterus that we have examined. The enlargement was noted first on rectal palpation Dec. 31, 1941, more than 10 months before autopsy. Measurements of a cross section of this uterus, when mounted on a slide, showed the greatest width to be 35 mm. The myometrium was 6 to 8 mm. thick.

The muscle bundles and fibrous tissue are normal, although perhaps the amount of muscular tissue may be relatively reduced. There are no myofibromatous nodules. Many of the larger arteries are extensively sclerosed, with loss of both media and intima. In several large veins there are organizing thrombi.

The endometrium is pulpy and, on section at autopsy, the soft spongy tissue prolapsed into the incised space.

The endometrium is very thick, the lumen being largely occluded by the mucosa. The main features of the endometrium are cystic and glandular hyperplasia with active endometritis (Fig. 3). Even in the numerous cystic glands the epithelium is high columnar, with cells in active secretion. Many of the glands are full of a clear secretion. Others contain much secretion and an abundance of leukocytes within the lumen of the gland. In many areas the largest cysts as seen in cross section are actually in the basalis. There is no atrophy of the epithelium even in excessively dilated glands, and the cells appear to be highly active. The arteries of the endometrium show no great amount of sclerosis, many of them appearing normal.

There is extensive squamous cell metaplasia of the cervix, of as great a degree as in monkey 779. There is also an area 5 mm. in diameter, near the external os, with active erosion. Epithelial plaques are desquamated and some areas are denuded of epithelium with masses of leukocytes, but few red blood cells, infiltrating among the epithelium and epithelial plaques.

The epithelium of the vagina is very thick, more than 30 cell layers, and cornified only in the outer one-fifth. There are heavy glycogen deposits in all cells above the basal layers and extending to the keratinized layer.

DISCUSSION

Since neither benign nor malignant tumors were found in the tissues examined the blastomatogenic activity of estrogen in this species of monkeys remains still unsettled. The dosage of estrogen administered was very large in relation to the amount that might be estimated to be the production by the normal mature monkey. The elapsed time was, perhaps, not over one-tenth of the potential life span of the monkey.

The cystic change that developed in the mammary glands of 2 of our 4 monkeys would seem to be a specific effect of the estrogen treatment. At least it bears a close similarity to the cystic changes that have been produced in the mammary glands of certain strains of mice by estrogen treatment (Haagensen and Randall). This mammary gland effect of estrogen has not been described previously in monkeys.

FIG. 3.—Endometrium of estrogen-treated monkey 780, showing cystic and glandular hyperplasia.

It is of interest to point out that cystic change in the breast following estrogen administration is seen chiefly in the strains of mice with a relatively low natural incidence of mammary cancer. In those with a high natural incidence epithelial proliferation, rather than cystic change, predominates (Haagensen and Randall). Monkeys do not seem to develop mammary carcinoma under natural conditions, and as a low cancer strain, cystic change is what might be expected in them on the basis of the evidence from the mouse experiments.

It had been observed previously (Overholser and Allen; Engle and Smith, 1935) that squamous cell metaplasia of the cervical mucosa was a specific effect of hyperestrinization.

Such massive replacement of the cervical mucosa as occurred in these monkeys has not been reported before. This change alone indicates that the estrogen was highly potent and long-acting. The changes in the cervix and the cystic and glandular hyperplasia of the endometrium, show that the treatment had sustained effects. Two monkeys, Nos. 779 and 780, had been under daily observation nearly 5 months after the last administration of estrogen. During this time no uterine bleeding occurred, such as is usual after the withdrawal of estrogen. After this lapse, even in No. 780, which had no ovaries, the uterus, cervix, and vagina showed the effects of estrogen stimulation, and no signs of genital atrophy.

The production of typical clinical cystic glandular hyperplasia of the endometrium of the monkey by estrogen only, without other manipulation, has not been reported previously, with the exception of one instance cited in an abstract by Hartman, Geschickter, and Speert. Such cystically dilated glands as have been described previously (Engle and Smith, 1938) were produced by continued estrogen–progesterone treatment. In other instances the effect of surgical interference may have modified the estrogen action. Dahl-Iverson, Hamburger, and Hjørdis have stated that no "Swiss cheese" type of endometrial hyperplasia occurred after as much as 15 months of treatment with total doses ranging up to 37 mgm. of estradiol benzoate, although there was some dilatation of single glands.

In view of the previous negative results, the pronounced response in the animals reported here indicates that the administered estrogens were highly effective, and that the effect was maintained in 2 monkeys for nearly 5 months after the last treatment.

Nelson has shown that small uterine fibromyomas can be induced in the guinea pig by estrogens, and Lipschütz and his associates have demonstrated that certain estrogens will induce subserous fibromas over the abdominal organs of the guinea pig. Lipschütz has recently reviewed the results of his work. No such changes could be observed either in the gross or microscopically in these monkeys. It is possible that there is a relative increase in the ratio of collagenous fibers to smooth muscle in the genital tract of these monkeys. An increase in fibrous tissue is usually thought to be related to the aging process alone, although Burack, Wolfe, and Wright have evidence that such an increase can be intensified in the uterus of the rat by extended estrogen administration. There were, however, no fibromyomatous nodules or fibromas in these monkeys, either in the genital tract or on other viscera.

Adenomatous development was not observed. Intensive invasion of the mucosa of the cervix uteri by squamous cell metaplasia, and glandular cystic endometria are the only changes in histopathology that can be referred to as effects of hyperestrinism. These alterations ensued even though the total dosage of the implanted pellets was not released, because of extrusion or encapsulation.

SUMMARY

Five aged female rhesus monkeys (*Macaca mullata*) were treated with α-estradiol. This estrogen was administered either as crystals or pellets implanted subcutaneously, at intervals of 5 or 6 weeks during a period of 24 to 28 months. The total amount administered ranged from 575 to 825 mgm.

Histological alterations occurred in the mammary glands of 2 monkeys. Definite cystic changes occurred in the ducts, which were dilated to many times their normal diameter. The lining epithelium was normal, with no papillary or other proliferation. The acini of the glands of all the monkeys were normal. Pronounced cystic and glandular hyperplasia of the endometrium was present in 2 animals.

The cervix uteri of all animals showed extensive squamous cell metaplasia, extending throughout the endocervix and into the racemose glands.

No neoplastic changes occurred in any of the organs examined.

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Rhabdomyosarcoma

Rat Tumor 92, Institute of Cancer Research, Columbia University, New York*

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(Received for publication July 26, 1943)

HISTORY

This rat tumor, found November 20, 1920, at the Institute of Cancer Research, was located beneath the skin and attached to the ensiform process. It was diagnosed as a chondrorhabdomyosarcoma and described by Bullock and Curtis in 1922 (1). During the transplantation from rat to rat the cartilage elements early lost their power of differentiation. The cross striated elements persisted through 15 generations. "One tumor of the fifteenth transplantation produced very extensive lung metastases which contained a large amount of muscular tissue." The muscle elements grew rapidly in the various transplants and exhibited large numbers of mitotic figures. It was designated No. 92.

November 6, 1933, Drs. Bullock and Curtis kindly sent me 2 rats with tumors and I studied them at intervals during a period of $3\frac{1}{2}$ years. In 1935 (2) I reported that histological sections of the tumors sent me did not contain muscle elements. A personal communication from Dr. Bullock in July, 1936, stated that sections of their recent transfer tumors did not have muscle and that the tumor now appeared to be a mixed cell sarcoma.

In 1935 I reported that although the tube cultures set up from a 1933 tumor did not have recognizable muscle elements in the outgrowths or colonies, "the tumors produced by the inoculation of these colonies into rats contained without exception many large multinuclear giant cells of the rhabdomyomatous type."

Where did these muscle elements come from? Were they modified host muscle or were the malignant cells of our cultures myoblasts that had retained or regained the ability to form recognizable muscle giant cells and strands?

TRANSPLANTABILITY

Bullock and Curtis obtained 3 takes in 93 inoculations in the first generation, 5 in 48 inoculations in the second generation, and 80 per cent in the third generation. The percentage of takes increased after that. The tumor evidently arose in a mixed strain of rats.

Our experience with the tumor began after it was well established in 1933. We had about 90 per cent takes with 5 per cent regressions and 10 per cent non-takes. The tumors attained diameters of about 10 mm. in 7 to 12 days, 20 mm. in 10 to 14 days, and 30 to 65 mm. in 18 to 40 days, when the animals usually died.

GROSS PATHOLOGY

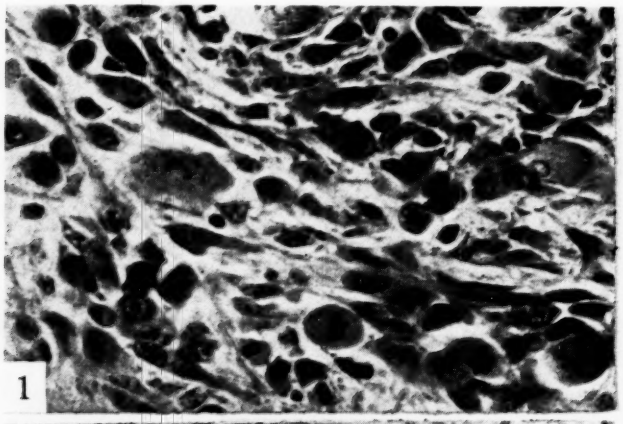
The most characteristic feature was a peculiar slimy mucoid substance that exuded from the cut surface when this was scraped, or smeared on slides for Wright's stain. The centers usually became necrotic when the tumors were 15 to 25 mm. in diameter. The tumors were firm, with a loose, spongy, necrotic center and a peripheral layer of good tissue 0.5 to 10 mm. in thickness. Scattered necrotic areas sometimes reached the surface and occasionally there was some reddish fluid.

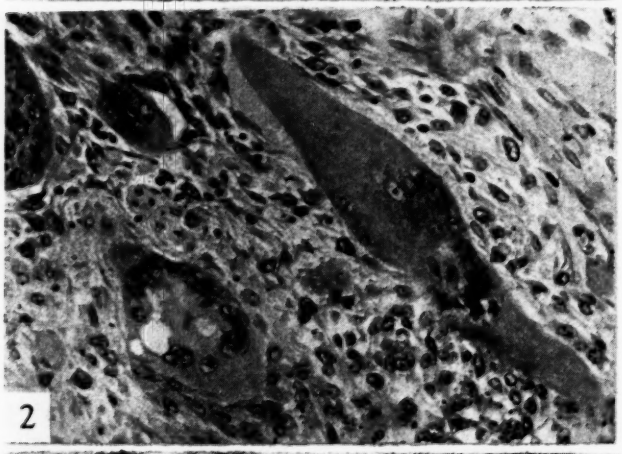
HISTOLOGY

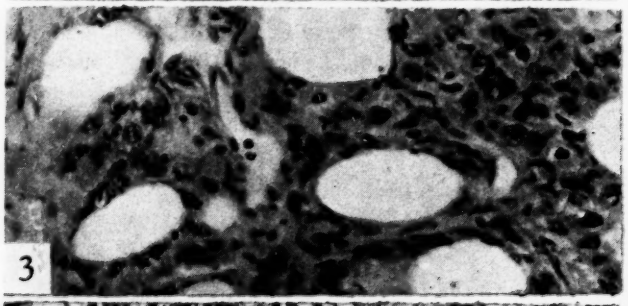
As already noted our histological sections of the two tumors sent from the Institute of Cancer Research, and fixed on November 6 and November 15, 1933, did not contain muscle giant cells (Fig. 1). The polyhedral and short spindle-shaped malignant cells are easily recognized by the deep staining. The large masses are host muscle fibers that are in the process of being destroyed by the malignant cells.

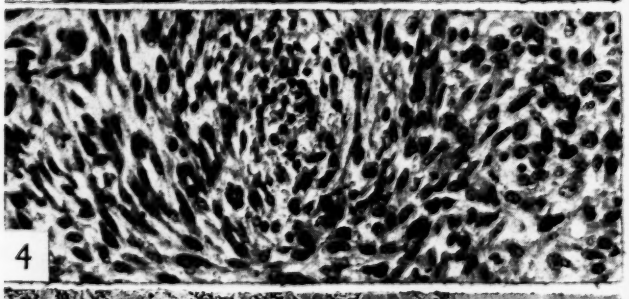
Sections and smears stained by Wright's method, of tumors produced by the inoculation of pure colonies of malignant cells carried in roller tubes for 105 to 189 days showed from few to many giant muscle cells without cross striations (Fig. 2). They were similar to the ones figured by Bullock and Curtis (1) and to those in many dibenzanthracene mouse tumors (3). Giant cells were found in the fifth generation of

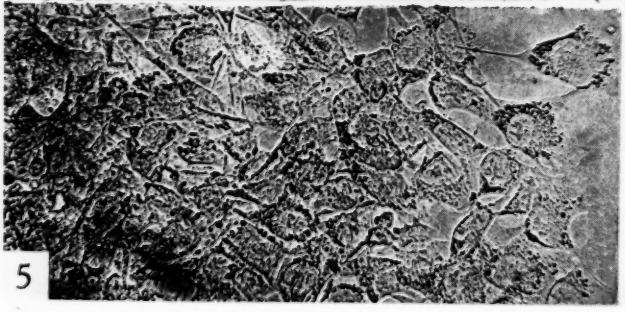
* This investigation was aided by a grant from The International Cancer Research Foundation.

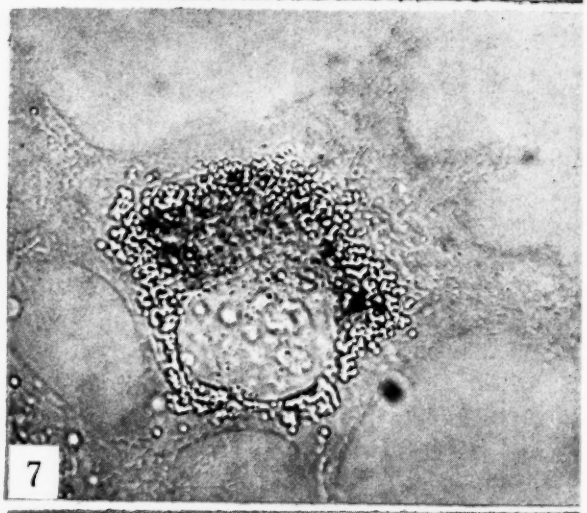


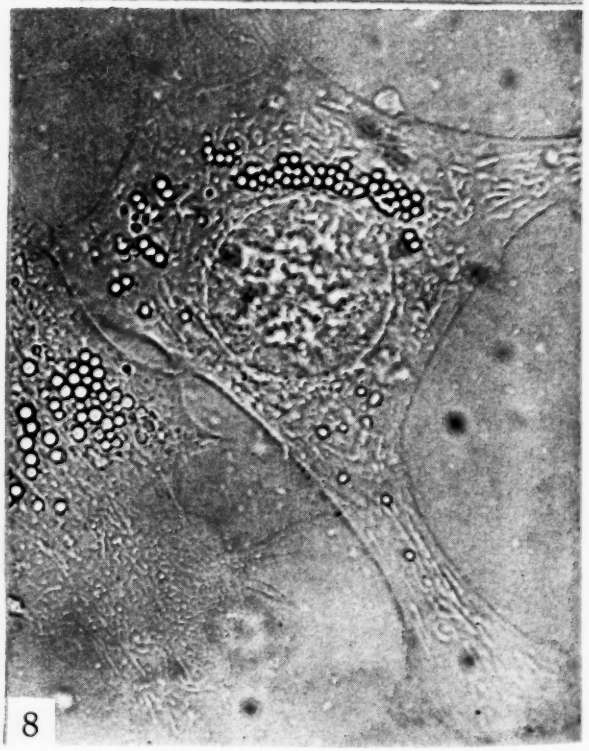












FIGS. 1-8

animal-to-animal transfers of one of the tumors. In addition to the giant cells there were many typical polyhedral and short spindle-shaped malignant cells of different sizes each with a single nucleus. There were all gradations in size from the latter to giant cells with many nuclei. The giant cells varied in shape from globular masses to elongated strands. The giant cells were evidently derived from the single nucleated cells either by fusion or by mitotic or amitotic division of the nuclei with compensatory increase of the cytoplasm. No mitotic divisions of nuclei have been found in the giant cells, yet mitoses were abundant in the uninuclear cells. There were indications of fusion but fixed material did not afford definite proof for this or for amitosis.

Sections of a second generation tumor (Fig. 3) produced by colonies from a 478 day roller tube contained only a few small giant cells in one region. This would seem to indicate that after prolonged cultivation the malignant cells lost most of their ability to form giant cells, at least temporarily, or that this ability ceased earlier in these transfer tumors than in the tumors produced by earlier tube cultures where giant cells were numerous even in a fifth generation tumor.

A tumor (Fig. 4), produced by the inoculation of a 571 day tube culture of the same lineage as the preceding tube cultures used for inoculations, had no giant cells in the sections. The malignant cells were more spindle-shaped than in the preceding tumors and formed wide bands of cells as in fibrosarcomas. Although sections of this tumor were quite different from the preceding ones the tumor was produced by the same type of malignant cell as the others.

Figs. 1 to 4 illustrate how differently malignant cells may behave *in vivo*.

The first and second transfer tumors from a tumor produced by the inoculation of colonies of an 817 day tube culture of the same lineage as the preceding tubes did not have recognizable muscle elements. The sections showed at the periphery typical polyhedral and short spindle cells. Deep regions of the section consisted of spindle cells arranged in bands as in fibrosarcomas.

Mitoses of malignant cells were common in all sections. None were found in the giant cells.

It was not possible to determine the identity of the malignant cells in the histological sections; that is, whether they were malignant myoblasts or fibroblasts. The deep staining suggests that they may have been myoblasts.

Wright's Smears

Wright's smears from tumors without giant cells in the sections had no giant cells. Smears from tumors with giant cells had from few to many giant cells, the number varying roughly with the number seen in the sections. They varied in size from small binucleate ones to large globular masses, about 200 microns in diameter, with many nuclei, and in shape from globular masses to elongated strands. No nuclei in mitosis were found in the giant cells. There was evidence that some of them were in the process of formation by fusion. There were many short spindle

DESCRIPTION OF FIGURES 1 TO 8

Fig. 1.—Tumor of November 15, 1933. The dark polyhedral malignant cells are easily recognized. The large masses are cross sections of muscle fibers that have been split apart by host tissue and are in the process of being destroyed. Cross sections of myofibrillae are still visible. Some small macrophage nuclei are scattered through the field. Deeper regions of the section show bands of fibrous tissue separating the polyhedral cells into areas. Necrosis begins in the centers of these areas. × 400 dia.

Fig. 2.—Tumor produced by the inoculation of pure colonies of malignant cells from a roller tube set up from the tumor of November 6 and carried for 172 days. Muscle giant cells, some with vacuoles, and numerous polyhedral and short spindle-shaped malignant cells predominate. Deeper areas of the section show numerous interlacing fibrous bands separating malignant cells into groups of various sizes. × 200 dia.

Fig. 3.—Third generation tumor. The first generation tumor was produced by the inoculation of colonies from a 478 day roller tube of the same lineage as the one that produced the tumor shown in Fig. 2. The section shows that the polyhedral malignant cells have invaded fat tissue. Deeper regions of the section show fibrous bands separating the polyhedral cells into areas of various sizes and much necrosis. The smallest necrotic areas are at the centers of the tumor cell areas. There are a few small giant cells in one area of the section. × 200 dia.

Fig. 4.—Tumor produced by pure colonies of malignant cells from a 571 day roller tube culture of the same lineage as the ones that produced the tumors shown in Figs. 2 and 3. There are no giant cells. The spindle-shaped malignant cells are closely packed together into wide bands. × 200 dia.

Fig. 5.—Migratory zone of a 1 day hanging drop culture, chicken plasma. Set up from transfer tumor, December 1, 1933. Malignant cells and a few macrophages. × 200 dia.

Fig. 6.—Living malignant cells in a 3 day hanging drop culture, chicken plasma. Set up from the tumor of November 6, 1933. Two malignant cells with indented nuclei, many fat globules, large central area, and granular mitochondria. Retouched. × 1,000 dia.

Fig. 7.—Living malignant cell in a 6 day hanging drop culture, chicken plasma plus neutral red. Set up from a 464 day roller tube culture. Periphery retouched. × 1,000 dia.

Fig. 8.—Living malignant cell in a 1 day hanging drop culture, chicken plasma 2 parts, plus human cord serum 2 parts, plus beef embryo extract 1 part. Set up from a 1,276 day roller tube culture carried by Mrs. Gey for the last 704 days. The cells of the culture are larger and in better condition than those in the two preceding cultures. Periphery retouched. × 1,100 dia.

and polyhedral cells with rather deeply staining cytoplasm, the probable precursors of the giant cells. They exhibited numerous mitoses. In addition to the above there were numerous macrophages with small nuclei and small spindle cells with pale cytoplasm, probably fibroblasts and endothelium.

One can get as good an idea of the number and character of the giant cells of a tumor by smears as by histological sections and in a shorter time.

Roller Tube Cultures

Roller tube cultures were set up November 6, 1933, and carried continuously without much difficulty for several years, sometimes in our laboratory and sometimes in Dr. Gey's. The colonies can be carried indefinitely and can be multiplied by dividing and replanting into fresh tubes. Media consisting of different combinations of chicken plasma, embryo juice, serum, and saline were used. The colonies were replanted into fresh tubes at irregular intervals.

The cells retained their malignancy and essential cytological characteristics. The outgrowth patterns were not especially characteristic. They differed somewhat from those of ordinary malignant fibroblasts. Recognizable muscle elements were not noted in any of the cultures, which after a few weeks consisted of only one type of cell. Yet some of the tumors produced by them contained many large muscle giant cells.

About 70 per cent of the inoculations of colonies into rats produced tumors. The failures were probably due to the use of mixed strains of animals. All the tube cultures used for inoculations and hanging drop cultures were lineal descendants of one tube set up November 6, 1933.

Cytology

The cytology of the living malignant cells as seen in hanging drop cultures remained remarkably constant during a period of more than $3\frac{1}{2}$ years. The hanging drop cultures were set up from the following material: (a) tumors taken from rats sent to me by the Institute of Cancer Research and used on November 6 and November 15, 1933, and October 12, 1936; (b) a number of transfer tumors from them; (c) tumors produced by the inoculation of 105 to 571 day old roller tube cultures; (d) a number of transfer tumors from them; and (e) colonies of cells taken directly from roller tubes after 66 to 1,276 days of continuous culture. The media consisted of chicken plasma, chicken plasma plus rat serum or rat plasma, and chicken plasma plus serum plus embryo juice. Sometimes a little neutral red was added.

As the cells migrated from the explants onto the cover glass they spread out into rather characteristic but constantly changing shapes. They became more or less isolated from one another at the periphery of the culture where they had more space (Fig. 5). Spindle forms were rare. Figs. 6, 7, and 8 are fairly representative. Every visible feature was subject to considerable variation, presumably as a result of changes in the condition of the cells due to the effects of different environments over different periods of time. In spite of these differences in shape, in size, in the number of fat globules, neutral red granules and vacuoles, and mitochondria, in shape and size of the nucleus and nucleoli, the size of the central area, etc., the cells seem to be of one type. Cells with 2 to 5 nuclei were common. Tripolar mitoses were rare. Pinocytosis was common in some cultures, absent in others.

There is nothing special about these cells to suggest that they may be malignant myoblasts. But since our knowledge of the behavior and cytology of malignant myoblasts is practically nil one cannot be certain of their identity. They were more like some types of malignant fibroblasts, or what have been assumed to be malignant fibroblasts, than like normal myoblasts found in cultures of skeletal muscle.

DISCUSSION

The history and the preceding observations indicate that this tumor was originally a rhabdomyosarcoma and suggest that the recognizable muscle elements dedifferentiated and split up into myoblasts; that some of the myoblasts on cultivation for 3 to 5 months regained their power to form, when inoculated into rats, muscle giant cells and muscle strands without cross striations, either by fusion or by amitotic division of the nuclei or by a combination of the two processes; that on further cultivation for a year or more the myoblasts lost this power at least temporarily even though they retained their essential visible cytological characteristics and their malignancy.

The only other possible source of the muscle giant cells in the tumors produced by the inoculation of cells from the tube cultures was the host muscle. Host muscle is frequently injured during inoculation, but among many fibrosarcomas produced in the same manner muscle giant cells have not formed. So this source can be ruled out.

SUMMARY

Rat tumor 92, Institute of Cancer Research, Columbia University, originally a chondrorhabdomyosarcoma, lost the chondrogenous part after a few rat-to-rat transfers and years later the muscle elements also disappeared.

Malignant cells, obtained from a tumor without recognizable muscle, produced after 3 to 6 months' cultivation in roller tubes pure colonies of cells that gave rise, when inoculated into rats, to tumors with few to many muscle giant cells. After 400 to 600 days' cultivation the cells produced tumors but no giant cells. The malignant cells, probably myoblasts, regained on cultivation and then lost, perhaps temporarily, their ability to form giant cells.

The living malignant cells in hanging drop cultures from all tumors and from tube cultures up to $3\frac{1}{2}$ years' cultivation, were essentially alike, except for the usual variations.

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The Retention of Radioactive Phosphorus in Leukemic Patients*

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(Received for publication August 1, 1943)

The use of radioactive phosphorus in the therapy of leukemia (1) is based on several considerations. The radioactive phosphorus gives off beta radiations, to which the leukemic cells are more sensitive than are many of the normal body cells. Its concentration in the tissues is relatively greater in rapidly proliferating cell groups such as leukemic infiltrations than in most normal tissues. The tissues that normally take up relatively larger amounts of P^{32} are those in which leukemic deposits tend to occur, such as liver, kidney, and bone. The half life of radio active phosphorus (14.3 days) is of convenient length for carrying out the necessary chemical manipulations in the preparation of the material and for delivering an adequate dosage of radiation without subjecting the tissues to radiation for months and years after its administration, as in the case of radium salts. P^{32} after giving off beta radiation changes to sulfur. The amount of phosphorus administered, usually as Na_2HPO_4, has no demonstrable effect aside from its radioactivity.

The present study, based on 69 cases, is planned to make available data on the effective radiation obtained by various doses of radioactive phosphorus.

The materials used in these observations have been prepared in two ways—by bombardment of red phosphorus by the cyclotron, or by the bombardment of an iron phosphide probe, placed in the beam of the cyclotron.[1] This latter method is preferable in that it gives a higher specific activity of the phosphorus. In several of the lots used, the activity has been of the order of 1 mc. per mgm. Even in the samples of relatively high specific activity, it must be remembered that only a small portion of the phosphorus present is radioactive.

Two facts must be kept in mind in attempting to evaluate radiation by P^{32}. First, although the measurements are expressed in millicuries, the radiations are actually beta rather than gamma, and hence not comparable directly with the gamma radiation of radium or radon; second, the range of the beta particles may vary materially, a very few penetrating tissue as far as 13 mm. from the atoms which are their source, while most have only a very short range (2). A further difference between the radiation administered by the conventional x-ray therapy apparatus and that administered by means of artificially radioactive phosphorous is that in the case of radiation from the x-ray tube there is appreciable variation in the amount of effective radiation with the depth of a given tissue beneath the skin; whereas with ingested or injected temporarily radioactive materials, the distribution of radiation is homogeneous throughout the body except as influenced by the specific affinity of certain tissues for the material.

In most of the cases studied in this series each gram of body tissue would receive about 120 ergs in the first 24 hours, assuming a homogeneous distribution of the phosphorus.[2]

The "threshold" dose of P^{32}, so far as effect on the blood cells is concerned, is said to be 0.006 to 0.009 μc. per gm. of body weight (3).

Two methods of administration of radioactive phosphorus have been utilized, the oral and the intravenous. I have customarily used the intravenous method and have used oral administration only to obtain comparative data. My preference for the intravenous method is based on the following considerations: first, the loss of about 20 per cent of the administered radioactive phosphorus due to precipitation and failure of absorption in the gastrointestinal tract is eliminated; second, the dosage can be determined accurately since all the material given reaches the blood stream; third, a higher level of concentration in the blood relative to the dose administered may be reached than is achieved by the oral method.

For intravenous administration a desired dose of P^{32} in the form of disodium phosphate is dissolved in 200 to 300 cc. of 5 per cent glucose and 0.85 per cent saline solution, or of normal saline solution alone. In

* This investigation was aided by a grant from The International Cancer Research Foundation.

[1] I am indebted to the Harvard Cyclotron Committee, to Professor Robley D. Evans, of Massachusetts Institute of Technology, and to Professor Ernest O. Lawrence for supplies of P^{32}.

[2] Based on calculations by Low-Beer, Lawrence, and Stone (2).

case of infants or children, it is dissolved in from 25 to 100 cc. of normal saline solution. The solution should be pyrogen free and autoclaved. If radioactive phosphorus obtained from the bombardment of red phosphorus is utilized, one or more recrystallizations as disodium phosphate are desirable in order to purify the compound. Sometimes traces of indicator left over from the chemical manipulations are present, which, in my experience, have been associated with febrile reactions on administration. There should be no untoward reaction to intravenous administration of properly prepared solutions.

The rate of administration may be fairly rapid, up to 10 or 15 cc. a minute in the case of adults. No special precautions are needed for the protection of the personnel administering the intravenous solution, since the bulk of radioactivity is screened out by the glassware and tubing, and they are in contact with even this weak source of radiation for only a short period of time.

I have not deemed it necessary to maintain the patients on a low phosphorus or low calcium diet when the intravenous mode of administration is utilized.

When P^{32} is to be administered orally, I have commonly given it in 200 cc. of orange juice.

In any studies of excretion, the difficulty of obtaining all the urine and feces from a given patient can be readily appreciated. Fortunately, the personnel in this hospital has been thoroughly drilled in the accurate and complete collection of excretions because of the large number of diabetic patients that have been treated here over many years. I believe that our figures on excretion, even though some of them cover a period of a month or more, are fairly accurate.

The measurements of radioactivity have been carried out on urine by determinations of dried aliquot samples; on blood and its constituents by drying the entire sample obtained and then measuring its activity; the measurements on feces have been made after ashing the entire fecal mass. Most of the measurements have been made on a modified type of Geiger counter, the remainder on an electroscope. A number of the samples have been read on both instruments with satisfactory checks obtained. The determination is accurate within 10 per cent as low as 0.001 μc.

Several leukemic patients had long-continued observation in the hospital in the course of treatment. One of these was followed for 33 days and one for 19 days. The results of the determinations on these patients are presented in the form of graphs on semilogarithmic paper, the total radioactivity remaining in the body being expressed as percentages of the initial total dose plotted against time. (Figs. 1 and 2). The sharp rises in the graphs represent the effect of supplemental doses of P^{32}. The rate of fall represents both excretion and decay of radioactive phosphorus.

It will be seen that the rate of fall in the amount of material retained is fairly constant, and the downward slope of the graphs essentially similar following each injection. At the end of 3 days about 75 per cent of the dose is still present. This is in keeping with the results obtained by Low-Beer and Treadwell (3).

The essential similarity of the amount retained at a given time after initial dosage is shown by Fig. 3, case 39 (chronic myelogenous leukemia), in which the percentage of retention of material administered is plotted against time. Here 8 doses ranging from 2,300 μc. to 130 μc. given a single patient are shown. The essential similarity of the slopes, in spite of wide variations in the amounts administered and the clinical condition of the patient, is clearly shown. Two of these doses, those of October 31 and November 11, 1942, were oral. The rest were intravenous.

Thus in case 39 an average of 87 per cent of the dose of radioactive phosphorus administered is present at the end of 24 hours, 80 per cent at the end of 48 hours, 75 per cent at the end of 72 hours, 63 per cent at the end of 120 hours, and 52 per cent at the end of a week. During the time that these doses were administered the patient's condition ranged from moribund to moderate activity, and the white blood cell count from 350,000 to 23,500. The red blood cell count ranged from 1,290,000 per cu. mm. to 4,400,000 per cu. mm.

The fastest excretion, September 28, 1942, was from a dose that was given at a time when the patient's white cell count was falling rapidly, from 310,000 per cu. mm. to 122,000 in 3 days. On the third day a blood transfusion of 500 cc. was given. The blood transfusion and rapidity of the destruction of the white cells may account for the greater excretion of this particular dose than the others.

The fairly constant rate of excretion is further shown in Fig. 4, case 34 (chronic myelogenous leukemia).

In Fig. 5 are presented 91 determinations of radioactivity of the blood made on 7 leukemic patients. This shows the fairly uniform rate of loss of radioactive material from the body when it is administered intravenously. The low points in Fig. 5, representing rapid excretion, were obtained from a patient with benzol poisoning and a leukemoid blood picture. The diagnosis of subacute leukemia had been made at one hospital and a diagnosis of myeloid metaplasia at another. In order that the discrepancy shown by this patient from the clearly leukemic group may be presented more plainly, 3 successive injections are presented in Fig. 6, illustrating not only the definite variation from the bulk of the leukemic patients, but also the variation from one dose to another.

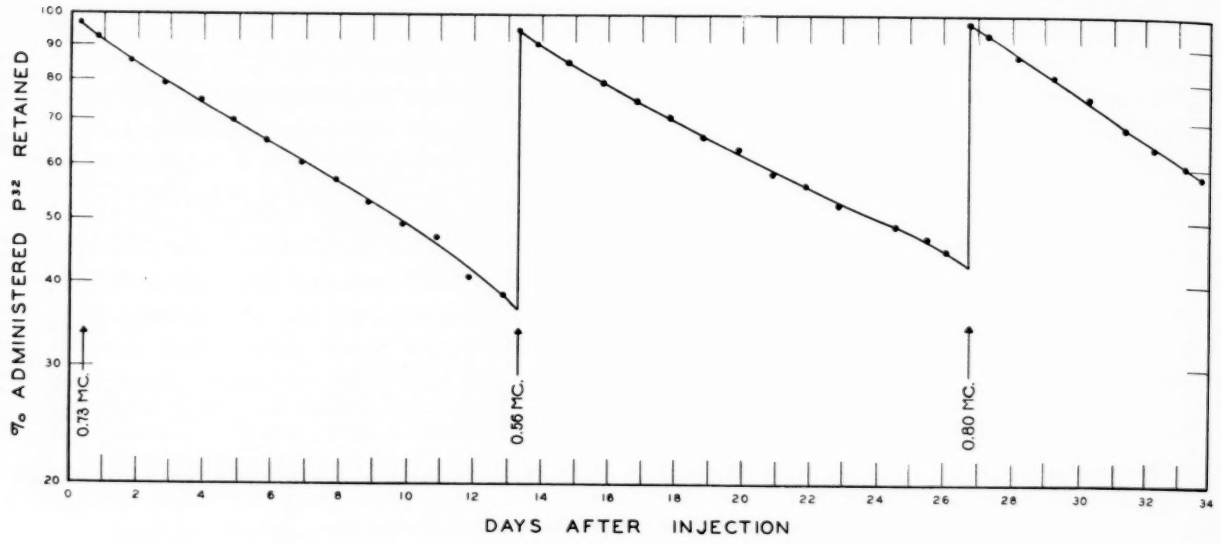

FIG. 1

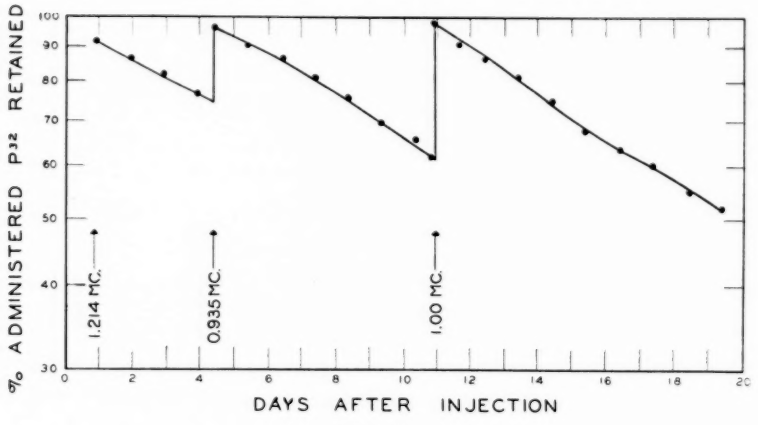

FIG. 2

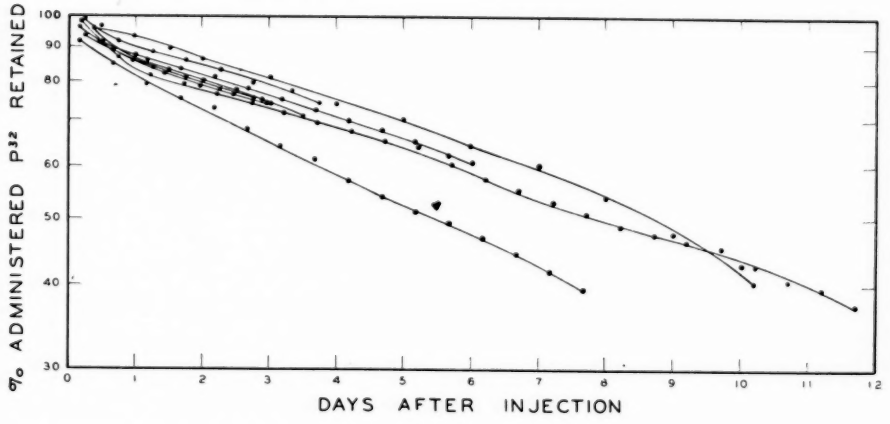

FIG. 3

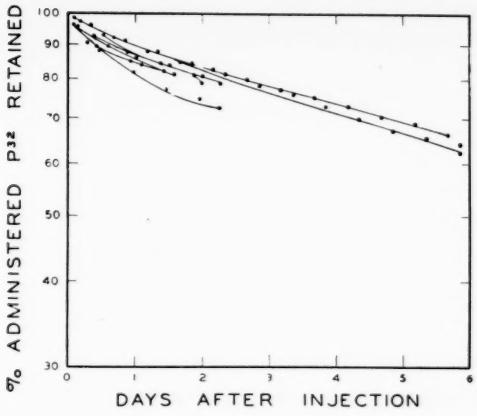

FIG. 4

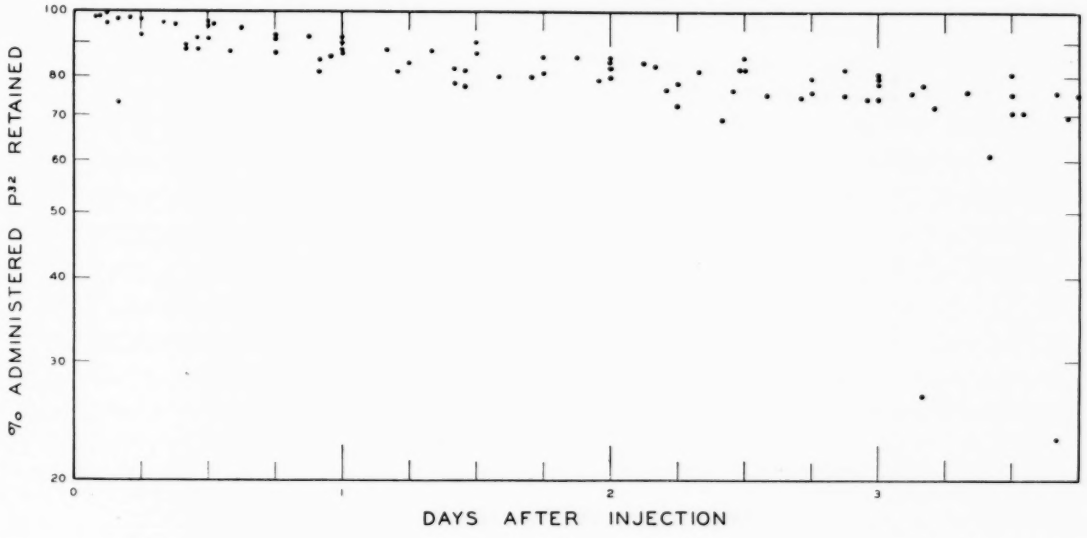

FIG. 5

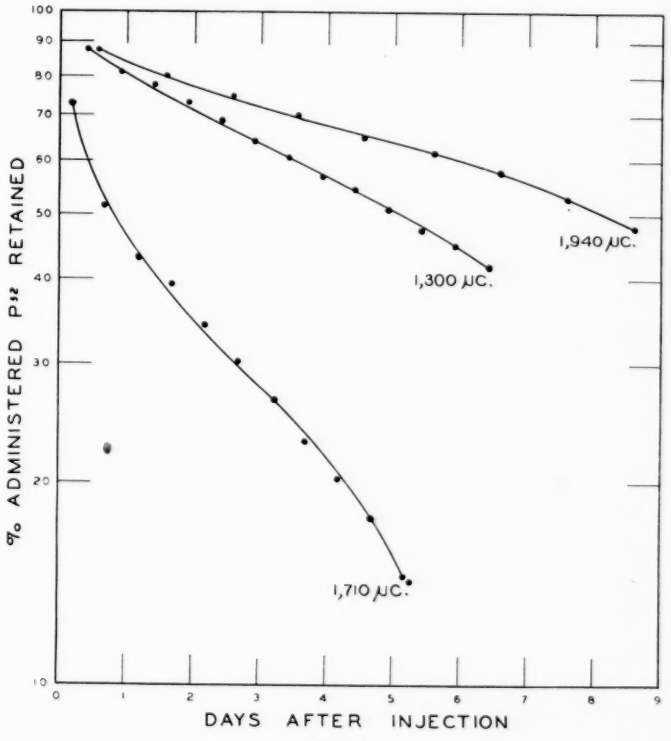

FIG. 6

The amount of fecal excretion is practically negligible when P^{32} is injected intravenously. This is brought out by random selection of sample determinations, given in Table I. If hemorrhage occurs into the gastrointestinal tract, the amount of P^{32} in the feces will be increased.

TABLE I: FECAL EXCRETION FOLLOWING INTRAVENOUS ADMINISTRATION

Case No.	Dose, μc.	Feces collected, days	Total P^{32} in feces, μc.
15	1,214	5	4.45
24	666	6	4.90
27	1,550	1	0.5
33	3,080	3	12.1
34	1,710	4	4.5
45	1,240	2	3.9
69	2,550	6	6.6

Although a slight amount of P^{32} is excreted in the saliva, this is usually swallowed and the major part reabsorbed. In case 1 the saliva contained 0.042 μc. per cc., 1½ hours after injection of a dose of 2,606 μc., when the blood level was 0.04 μc. per cc.

SUMMARY AND CONCLUSION

1. The retention of radioactive phosphorus when administered intravenously in cases of leukemia is relatively constant, amounting on the third day to 75 per cent of the original dose and on the seventh day to 52 per cent.

2. The rate of excretion of P^{32} by leukemic patients does not vary significantly with variation of doses within the therapeutic range, nor with the clinical condition of the patient.

3. A blood dyscrasia of undetermined nature gave abnormally rapid excretion rates.

4. The amount lost in the feces is negligible when radioactive phosphorus is administered intravenously.

I am indebted to Mr. Russell F. Cowing for the physical measurements utilized in this paper.

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1. LAWRENCE, J. H., SCOTT, K. G., and TUTTLE, L. W. Studies on Leukemia with the Aid of Radioactive Phosphorus. Internat. Clin., **3**:33-58. 1939.
2. LOW-BEER, B. V. A., LAWRENCE, J. H., and STONE, R. S. The Therapeutic Use of Artificially Produced Radioactive Substances; Radiophosphorus, Radiostrontium, Radioiodine, with Special Reference to Leukemia and Allied Diseases. Radiology, **39**:573-597. 1942.
3. LOW-BEER, B. V. A., and TREADWELL, A. DE G. Clinical Studies with the Aid of Radio-Phosphorus. V. Early Effects of Small Amounts of Radio-Phosphorus on Blood Cell Levels, Uptake and Excretion. J. Lab. & Clin. Med., **27**:1294-1305. 1942.

Abstracts

Experimental Research, Animal Tumors

A Sarcoma-Producing Factor Extractable from Transplanted Rat Fibrosarcomas. APTEKMAN, P. M., KING, H. D., and LEWIS, M. R. [Wistar Inst., Philadelphia, Pa., and Carnegie Inst. of Washington] *Cancer Research,* **3**:856-857. 1943.

Rat sarcomas that had been transplanted through 20 to 40 passages in inbred albino rats and had grown in 100% of the animals were used for these studies. Fat was extracted by means of benzol from excised sarcomas and from the livers of rats bearing this tumor. The extracted fat was injected into young rats of the susceptible strain. Spindle cell sarcomas developed at the site of injection in 5 animals given fat extracted from the sarcomas, and in 2 animals given fat extracted from the livers. In addition to the 7 sarcomas, epithelial tumors developed in 2 of the treated rats in the mammary glands near the site of injection of the extracted fat.—Authors' abstract.

Chemical Studies on the Mode of Action of Methylcholanthrene on Mouse Epidermis. CARRUTHERS, C., and SUNTZEFF, V. [Barnard Free Skin and Cancer Hosp., St. Louis, Mo.] *Cancer Research,* **3**:744-748. 1943.

Studies on the influence of methylcholanthrene upon epidermal iron, calcium, sodium, magnesium, potassium, and ascorbic acid are described. Mice were painted on alternate days with a benzene solution of methylcholanthrene. At various periods from 10 to 60 days after the beginning of treatment, samples of epidermis were removed for chemical analysis from mice that had received from 1 to 24 applications of the carcinogen. Both untreated and benzene-treated epidermis served as controls. One treatment with the carcinogen reduced within 10 days the iron and calcium nucleoprotein phosphorus ratios to approximately 50% of the normal. Multiple applications produced a further lowering in the iron nucleoprotein ratio, while the reduction in the calcium ratio remained rather constant. On the other hand the sodium, potassium, and ascorbic acid nucleoprotein phosphorus ratios were not appreciably altered, while there was a slight increase in the magnesium nucleoprotein phosphorus ratio. The significance of the chemical changes is briefly discussed.

The existence of "precancerous" tissue from a chemical standpoint is postulated. The mineral analysis of mouse epidermis is also given, and the use for other biological problems of the technics employed in these studies is briefly mentioned. Four tables and 1 figure are appended.—Authors' abstract.

The Effect of Oxygen on the Fluorescence of Certain Hydrocarbons. MILLER, J. A., and BAUMANN, C. A. [Univ. of Wisconsin, Madison, Wis.] *J. Am. Chem. Soc.,* **65**:1540-1546. 1943.

The intensity of fluorescence was measured for certain carcinogenic and related hydrocarbons; namely, 3,4-benzpyrene, 20-methylcholanthrene, 9,10-dimethyl-1,2-benzanthracene, 1,2,5,6-dibenzanthracene, 1,2-benzanthracene, and anthracene, each in several solvents in air and *in vacuo*. In air the intensities usually ranged from one-half to one-sixth of those observed *in vacuo* (absence of all gas but solvent vapor). Most of the difference was due to dissolved oxygen, although in some cases the degree of quenching did not parallel oxygen solubility. In the presence of oxygen the fluorescence bands of benzpyrene were diminished in intensity, but both the fluorescence and absorption spectra were qualitatively the same in air and *in vacuo*. In contrast the fluorescence of the unsaponifiable matter from mouse tissue did not vary greatly with Po_2 either in petroleum ether or in pyridine.

SO_2 was many times as effective an inhibitor of fluorescence as O_2; HCl and $N(CH_3)_3$ were less effective. The inhibition was reversible by changing the partial pressure of the gas. Sulfur, nitrobenzene, and tetranitromethane inhibited the fluorescence of benzpyrene solutions both in air and *in vacuo*. This inhibition could be reversed by passing the quenched solution through a column of aluminum oxide. Na, H_2, CO_2, CO, H_2S, NH_2CH_3, and NH_3 failed to affect the intensity of fluorescence of benzpyrene.

The fluorescence intensities of the hydrocarbons varied hyperbolically with the partial pressure of oxygen. The equation, $F=\frac{a}{1+bPo_2}$, relating these two quantities was derived from either of the alternate assumptions that a nonfluorescent dissociable complex formed between oxygen and the hydrocarbon or that the quenching of fluorescence by oxygen was a collision phenomenon. Observed values agreed well with values calculated from the derived equation. Apparently, therefore, the effect of oxygen on fluorescence is not a capricious one, but extremely regular and reproducible.—Authors' abstract.

The Determination of Carcinogenic Hydrocarbons in Animal Tissue. Two-Condition Fluorometry. MILLER, J. A., and BAUMANN, C. A. [Univ. of Wisconsin, Madison, Wis.] *Cancer Research,* **3**:849-855. 1943.

The fluorescence of the carcinogenic and related hydrocarbons has the following properties pertinent to a quantitative determination. It is stable, reproducible, and of sufficient intensity for the accurate measurement of 1 μgm. of hydrocarbon or less. It varies directly with con-

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centration. It is resistant to alkali and differs significantly from the fluorescence of animal material in such qualities as intensity and spectral distribution. The fluorescence of the hydrocarbons is strictly additive to the fluorescence of the unsaponifiable matter of animal tissue and is much more sensitive than the latter to solvent or to oxygen.

On the basis of these properties, a system of two-condition fluorometric analysis was devised and applied to the determination of the carcinogenic hydrocarbons in animal tissue. The hydrocarbon was separated from the treated tissue in the unsaponifiable fraction and most of the tissue fluorescence eliminated by selected filters. The remaining interference was eliminated by equations based on readings taken either in 2 selected solvents or under 2 different partial pressures of oxygen in the same solvent. Under these conditions the fluorescence of the hydrocarbon and of the unsaponifiable matter was changed unequally. The determination therefore was based on the differences in readings measured under the 2 experimental conditions employed. By either the two-solvent or the two-pressure technique it was possible to recover 1 μgm. or less of benzpyrene added to mouse tissue with average errors of 2 to 5%. The lower limit of the method appeared to be about 0.05 μgm. of benzpyrene.—Authors' abstract.

Experimentally Produced Fibroids in the Guinea Pig and Their Possible Analogy to Myomas in the Human Being. Marx, R., Glass, S., and Shulman, A. [Cedars of Lebanon Hosp., Los Angeles, Calif.] *Am. J. Obst. & Gynec.*, **44**:259-265. 1942.

The work of Lipschütz and other investigators on the experimental production of fibroids in guinea pigs by means of estrogenic substances was confirmed. The authors feel that further study of the experimental tumors might lead to an understanding of the genesis of human myomas. —A. K.

A Theory on the Origin of Cancer. Preliminary Report. Magnelia, A. L., Kaplan, J. H., and Hyson, E. [Rockford, Ill.] *Illinois M. J.* **83**:43-46. 1943.

On the theory that the presence or absence of growth-controlling hormones for specific tissues is a vital factor in balancing the pattern of tissue growth, and that the pregnant mother at term is the most abundant source of these hormones, urine from pregnant women at term and umbilical cord serum after severance were collected. These were used in the treatment of spontaneous breast tumors in mice, transplanted sarcoma 180 in mice, and a few human cases. The average life time of mice so treated was longer than untreated controls.—M. E. H.

Urinary Steroids from Breast Cancer Patients. Hill, B. R., and Longwell, B. B. [Univ. of Colorado Sch. of Med., Denver, Colo.] *Endocrinology*, **32**:319-326. 1943.

Androsterone, 3-α-hydroxyetiocholanone-17, an impure form of pregnanediol, cholesterol, and a hydrocarbon of low melting point were isolated from the urine of postmenopausal women with cancer of the breast or with metastases from breast cancer. Control urine was not analyzed, but comparisons were made with the results reported in the literature of analyses of urine of ovariectomized women, of normal women, and of cancerous men and women. On the basis of these comparisons the authors conclude that their findings do not constitute positive evidence that the compounds isolated bear a relationship to the existence of malignant growths.—C. A. P.

Estrogen Administered to Aged Female Monkeys with No Resultant Tumors. Engle, E .T., Krakower, C., and Haagensen, C. D. [Coll. of Physicians and Surgeons, New York, N. Y.] *Cancer Research*, **3**:858-866. 1943.

Five aged female rhesus monkeys (*Macaca mullata*) were treated with α-estradiol administered either as crystals or pellets implanted subcutaneously at intervals of 5 or 6 weeks during a period of 24 to 28 months. The total amount administered ranged from 575 to 825 mgm. Histological changes occurred in the mammary glands of 2 monkeys. Definite cystic changes were found in the ducts, which were dilated to many times their normal diameter. The lining epithelium was normal, with no papillary or other proliferation. The acini of the glands of all the monkeys were normal. Pronounced cystic and glandular hyperplasia of the endometrium was present in 2 animals. The cervix uteri of all animals showed extensive squamous cell metaplasia, extending throughout the endocervix and into the racemose glands. No neoplastic changes occurred in any of the organs examined.—Authors' abstract.

Spontaneous Testicular Tumors in Mice. Gardner, W. U. [Yale Univ. Sch. of Med., New Haven, Conn.] *Cancer Research*, **3**:757-761. 1943.

Although testicular interstitial cell tumors have appeared in estrogen-treated mice of several inbred strains, such tumors have not been described in untreated mice of similar origin. Among 61 untreated hybrid mice with 1 parent from the A strain, 3 testicular tumors were found. None were observed in untreated mice of the A strain. The life span of the mice of the A strain, however, was 200 to 300 days less than that of the hybrids. Two of the spontaneous testicular tumors resembled those observed in estrogen-treated mice, and one resembled a seminoma rather than the usual interstitial cell tumors. It was concluded that in mice of certain strains estrogens may act to reveal or augment tendencies to acquire testicular interstitial cell tumors that otherwise would not be attained during the usual life span.—Author's abstract.

Testicular Changes Resembling Early Stages in the Development of Interstitial Cell Tumors in Mice of the A Strain after Long-Continued Injections of Pregnant Mare Serum. Pfeiffer, C. A., and Hooker, C. W. [Yale Univ. Sch. of Med., New Haven, Conn.] *Cancer Research*, **3**:762-766. 1943.

Fifteen male mice of the A strain were given daily injections of 50 I.U. of pregnant mare serum, for periods ranging from 30 to 550 days, as one means of determining whether gonadotropic hormones mediate the changes that culminate in the development of interstitial cell tumors of the testis in estrinized mice of this strain. During the first 100 days there was a slight enlargement of the testes followed by a prolonged reduction in size. After 1 year's treatment normal testicular size was regained or slightly exceeded. The testes never acquired the yellow or brown color that characterizes the testes of estrogen-treated mice. The accessory glands of reproduction hypertrophied greatly, evincing the production of large amounts of androgen. In the testes of 9 of the treated animals the interstitial

cells formed nodules ranging in area from one-third to twice the cross sectional area of a tubule. The nodules were fairly well localized and occupied various positions, the most frequent being in the region of the mediastinum testis. These nodules resembled the young nodules in the development of testicular tumors in estrogen-treated mice. Local invasions were not seen, and lymph nodes were not involved. In the testes of 4 animals the interstitial cells were increased in number throughout the organ, but did not form nodules. In 2 animals no interstitial cell change was seen.—Authors' abstract.

The Effects of Lowered Body Temperatures on Methylcholanthrene Fibrosarcomas in Rats. Hill, R. M., Rutledge, E. K., Ware, A. G., Schultz, F. H., and Livingston, W. H. [Univ. of Colorado Sch. of Med. and Hosps., Denver, Colo.] *Cancer Research,* **3**:841-848. 1943.

The growth of methylcholanthrene fibrosarcomas in the thigh muscles of rats with normal body temperatures is compared with the growth of similar tumors in rats with low body temperatures. Hypothermia induced 3 times a week or less and lasting from 5 to 10 hours had no demonstrable effect. Intermittent hypothermia induced daily and continuous hypothermia of several days' duration had a retarding effect on tumor growth. Mean body temperatures of 20° to 24° C. were more effective than higher body temperatures.—Authors' abstract.

A Technic for the Production of Hypothermia in Albino Rats. Hill, R. M., Ware, A. G., and Schultz, F. H. [Univ. of Colorado Sch. of Med. and Hosps., Denver, Colo.] *Cancer Research,* **3**:839-840. 1943.

A method is described for the production and maintenance of hypothermia in rats. The method of taking temperatures is discussed.—Authors' abstract.

A Free Choice Dietary Study of Tumor-Bearing Rats. Cahill, W. M., Dunning, W. F., and Smith, A. H. [Wayne Univ. Coll. of Med., Detroit, Mich.] *Cancer Research,* **3**:830-832. 1943.

A free choice dietary study was carried out on tumor-bearing and on non-tumor-bearing rats. The animals were allowed to select their own diet from food supplies in separate cups containing carbohydrate (sucrose), fat (crisco), protein (casein), salts, yeast, and cod liver oil, respectively. Growth of the transplantable mammary adenocarcinoma (R 2426) in pedigreed rats of the pink-eyed agouti hooded August strain did not significantly alter the appetite of the animals for any particular unmixed dietary ingredient.—Authors' abstract.

Further Studies on the Tumor-Promoting Action of Fat. Lavik, P. S., and Baumann, C. A. [Univ. of Wisconsin, Madison, Wis.] *Cancer Research,* **3**:749-756. 1943.

Tumors were induced in the skin of mice and rats by the local application of methylcholanthrene. The various groups of animals received, in addition, some special dietary treatment.

The fatty acids of hydrogenated vegetable oil, prepared free from unsaponifiable matter and resynthesized into triglycerides, had essentially the same tumor-promoting activity as natural fat. The prolonged heating of several natural fats did not definitely alter their tumor-promoting activity.

Much of the effect of the dietary fat was exerted locally. The application of oil to the skin increased the total number of tumors produced, while fat that was fed as an emulsion in the drinking water was only about one-half as effective in increasing tumors as fat incorporated into the diet.

Possible products of fat metabolism, such as acetone, ethyl acetoacetate, and butyric acid, did not appreciably increase the incidence of the tumors in either rats or mice. An increased intake of riboflavin and protein failed to diminish the tumor-promoting action of the fat.

The experiments demonstrated also that increased dietary fat did not increase the incidence of sarcomas in mice due to the subcutaneous injection of methylcholanthrene, nor of spontaneous mammary tumors of rats, nor of induced tumors due to the injection of methylcholanthrene either subcutaneously or into the submaxillary gland of the rat.

Mice painted with methylcholanthrene consumed 12 to 30% more calories on diets high in fat than on corresponding low fat diets. A rough correspondence was observed between the caloric intakes of mice on the various rations and the numbers of tumors that ultimately appeared. On an equivalent caloric intake, the incidence of tumors in mice on the high and low fat diets was more nearly equal. It is suggested that at least part of the tumor-promoting action of fat is due to an accompanying increased consumption of calories.—Authors' abstract.

Presence in Various Grains of Factors Inhibiting Tumor Growth. Lewisohn, R., Laszlo, D., Leuchtenberger, C., Leuchtenberger, R., and Dische, Z. [Mt. Sinai Hosp., New York, N. Y.] *Proc. Soc. Exper. Biol. & Med.,* **52**: 269-272. 1943.

Groups of 7 mice are matched with respect to tumor size 7 to 10 days after inoculation with sarcoma 180. If one of these groups is injected intravenously with saline twice daily for 2 consecutive days, the tumor sizes and tumor weights of the injected animals and controls will agree after 48 hours. If a group is similarly injected with a standard yeast extract, the tumor growth in this group is significantly inhibited.

It was found that 4 intravenous injections of 0.1 cc. of standard yeast extract (corresponding to 5.25 mgm. solids) produced a significant inhibition of tumor growth if the mice were fed a normal diet. If, however, the mice were fed a polished rice diet, 4 injections of 1:75 mgm. solids of the same standard preparation produced a similar inhibition. A number of experiments indicated that the increased inhibition was not due to dietary deficiency nor caloric restriction. One tenth of a cubic centimeter of an aqueous extract of the rice, corresponding to 2.4 mgm. solids, inhibited tumor growth to about the same extent as did the standard preparation.

Similar feeding experiments were done with pearled barley, malted barley, wheat flour, wheat germ, oats, corn meal, and soya beans. The pearled barley and soya beans increased the inhibitory effect; the wheat flour, oats, and corn meal did so to a lesser extent; while no effect followed the feeding of malted barley and wheat germ.

Extracts of pearled barley produced inhibition similar to that effected by the standard preparation when groups of

mice were kept on a normal diet; a malted barley extract was ineffective.—M. B.

Treatment of Spontaneous Breast Cancers in Mice with Pearled Barley. Lewisohn, R., Leuchtenberger, C., Leuchtenberger, R., Laszlo, D., and Dische, Z. [Mt. Sinai Hosp., New York, N. Y.] *Proc. Soc. Exper. Biol. & Med.*, **52**:272-273. 1943.

A pearled barley extract is prepared as follows: To 100 gm. of barley, 1,500 cc. distilled water plus 0.15 cc. glacial acetic acid are added. The mixture is stirred, heated rapidly to 100° and boiled for 7 minutes. The supernatant fluid is decanted, cooled to room temperature, precipitated with 50% ethanol, kept in the cold overnight, and filtered. The filtrate is freed from ethanol in vacuum and concentrated to 30 cc. The turbid concentrate is filtered through a sterile Seitz filter. About 2.5% of barley solids were extracted. Intravenous injections of 0.1 cc. were given every day until the tumors disappeared completely. Mice of Strain A, the Swiss and Rockland Farm strains were used. They were fed pearl barley and carrots. After a few treatments, hemorrhagic tumors became whitish; hard tumors became soft, and often the whole tumor was expelled. Of 46 spontaneous breast adenocarcinomas, 19 tumors regressed completely.—M. B.

Vitamin A and the Toxic Action of Dibenzanthracene on the Tissues. Goerner, A., and Goerner, M. M. [Long Island Coll. of Med., Brooklyn, N. Y.] *Cancer Research*, **3**:833-838. 1943.

The protective action of various amounts of vitamin A against the toxic manifestations produced in rats by intraperitoneal injections of 1,2,5,6-dibenzanthracene was studied. The addition of increasing amounts of vitamin A to the injected dibenzanthracene brought about a decrease in the high mortality observed in animals treated with the hydrocarbon alone. Other toxic results caused by dibenzanthracene such as lack of growth, the continued destruction of hepatic tissues, and the depletion of hepatic stores of vitamin A gave place to a continuance of growth, the absence of severe liver damage, and an earlier renewal of vitamin A storage in the liver.—Authors' abstract.

The Influence of Egg White and Avidin Feeding on Tumor Growth. Kensler, C. J., Wadsworth, C., Sugiura, K., Rhoads, C. P., Dittmer, K., and du Vigneaud, V. [Memorial Hosp., and Cornell Univ. Med. Coll., New York, N. Y.] *Cancer Research*, **3**:823-824. 1943.

The administration of a diet rich in egg white and avidin to mice bearing spontaneous mammary carcinoma had no favorable effect on the course of the disease. The successful takes and subsequent growth of the Flexner-Jobling carcinoma and of mouse sarcoma 180 were not inhibited by a diet containing a high level of egg white.—Authors' abstract.

The Effect of Pyridoxine on Tumor Growth. Kline, B. E., Rusch, H. P., Baumann, C. A., and Lavik, P. S. [Coll. of Agric., Univ. of Wisconsin, Madison, Wis.] *Cancer Research*, **3**:825-829. 1943.

When the Flexner-Jobling carcinoma was implanted into rats partially depleted of pyridoxine, the percentage of takes was lower, the number of regressions higher, and the size of the tumors smaller than in control animals receiving the same number of calories. Similar results were observed with 2 types of transplantable mouse tumors: the Yale carcinoma 1, and a fibrosarcoma originally induced by ultraviolet light. A low percentage of tumors in each of the deficient groups grew as well as the average for the corresponding group on the complete diet.

The production of skin tumors in mice painted with methylcholanthrene was definitely retarded on a diet low in pyridoxine. This effect, also, was independent of caloric intake. Pyridoxine deficiency appeared to have less effect on the production of sarcomas due to the subcutaneous injection of methylcholanthrene.—Authors' summary.

Action of Bacterial Toxins on Tumors. IV. Distribution of Tumor-Hemorrhage Agents among Bacterial Species. Hutner, S. H., and Zahl, P. A. [Haskins Lab., New York, N. Y.] *Proc. Soc. Exper. Biol. & Med.*, **52**: 364-368. 1943.

The hemorrhage activity of concentrated bacterial cultures was tested on white male Rockland mice carrying 7 day old implants of mouse sarcoma 180. The bacteria were killed with a toluene-chloroform mixture, and the material to be assayed was given intraperitoneally. Tumor hemorrhage reached a maximum in 8 hours after injection of the toxin, at which time the mice were killed and the tumors examined.

Thirty gram-negative and 7 gram-positive bacterial species were tested for tumor hemorrhage activity. It was found that in general gram-negative forms induced tumor hemorrhage (exceptions: *Rhizobium, Phoeomonas, Streptococcus varians, Rhodobacillus palustris*); while this property was lacking in the gram-positive forms (exception: *Listeria monocytogenes*). Hemorrhage was also induced by the photosynthetic gram-negative purple bacterium *Rhodospirillum rubrum*. It is concluded that toxins inducing tumor hemorrhage, and probably bound up in the complex O antigens, are characteristic of gram-negative bacteria.—M. B.

Chemotherapeutic Studies on Transmitted Mouse Leukemia. Flory, C. M., Furth, J., Saxton, J. A., Jr., and Reiner, L. [Cornell Univ. Med. Coll. and New York Hosp., New York, N. Y., and Burroughs Wellcome & Co., Tuckahoe, N. Y.] *Cancer Research*, **3**:729-743. 1943.

The effect of underfeeding, of x-rays, and of the administration of potassium arsenite, 4 organic arsenicals (neoarsphenamine, mapharsen, tryparsamide and soamine), of benzene and benzene derivatives (toluene, 3 xylenes, mesitylene, pseudocumene, ethelbenzene and cymene), and of stilbestrol, sulfadiazine and sulfaguanidine has been studied on transmitted myeloid and lymphoid leukemias in mice.

Each of 3 strains of myeloid leukemia responded differently to the therapeutic agents, but the prolongation of life of the leukemic mice caused by the administration of a given chemical or other agent was fairly constant for each strain. Benzene, potassium arsenite, and, to a lesser extent, underfeeding retarded the development of 1 strain of myeloid leukemia (No. 106). All 3 were ineffective against another strain (No. 1712), while only benzene was highly effective against a myeloid chloroleukemia (strain 1394). X-ray had some effect on the last 2 strains. The best results were obtained with benzene, which occasionally doubled or tripled the life span of the animals.

Some beneficial effect was manifest even when benzene was administered to mice with myeloid chloroleukemia (strain 1394) at an advanced stage of the disease. Benzene, underfeeding, and x-rays all prolonged the lives of mice with certain strains of lymphoid leukemia. The response was not related to the chronicity of the disease. No organic arsenical or benzene derivative was as effective as arsenite or benzene. Underfeeding alone retarded the development of most strains of leukemia, but many of the chemicals seemed to exert their beneficial effect without causing loss of weight. While sulfadiazine and sulfaguanidine did not significantly prolong the life of the leukemic mice, they did not harm the animals. These compounds may be of value in the treatment of infections complicating leukemias.—Authors' abstract.

Enhancement of Leukemogenic Action of Methylcholanthrene by Pre-Irradiation with X-Rays. Furth, J., and Boon, M. C. [Cornell Univ. Med. Coll. New York, N. Y.] *Science,* **98**:138-139. 1943.

Moderate and large doses of x-rays rapidly destroy blood-forming organs, but if irradiation is discontinued regeneration follows within a few days, and during this phase mitotic figures are numerous in blood-forming tissues. To test the possibility that the blood-forming organs might be particularly susceptible to leukemogenic agents during the regenerative phase, mice of the Rf/Ak stock, 4 to 6 weeks of age, were treated as follows: 36 mice were irradiated with 175 r over the entire body, and beginning the day following the irradiation, were painted with methylcholanthrene. Some of these animals developed leukemia at 3 to 4 months of age. The greatest incidence was at 5 months. In all, 64% of the treated mice developed leukemia. In a group of 37 mice given methylcholanthrene alone, leukemia developed later, beginning at 6 months, and the total incidence was much lower (16%). Finally, of a group of 18 mice treated only with x-rays (175 r), 1 mouse (6%) developed leukemia at 7 months.—R. B.

The Retention of Radioactive Phosphorus in Leukemic Patients. Warren, S. [Harvard Cancer Commission and New England Deaconess Hosp., Boston, Mass.] *Cancer Research,* **3**:872-876. 1943.

Radioactive phosphorus is a useful means of therapy of leukemia because of the concentration of the radioactive material in rapidly proliferating cells, its preferential deposition in those organs in which leukemic deposits tend to occur, and because of its convenient half life of 14.3 days. The data in the present study are based on 69 cases. The retention in the body of radioactive phosphorus administered intravenously was relatively constant. On the third day more than 75% of the original dose was present, and on the seventh day more than 50%. The rate of excretion of P^{32} is independent of dosage within the therapeutic range and apparently independent of clinical condition. Only a very slight amount is lost in the feces when radioactive phosphorus is administered intravenously.—Author's abstract.

The Importance of Dosage in the Intradermal Immunization against Transplantable Neoplasms. Gross, L. [Christ Hosp., Cincinnati, Ohio.] *Cancer Research,* **3**:770-778. 1943.

One hundred and ninety-five mice of the C3H inbred line were inoculated intradermally with a standard volume (0.02 cc.) of tumor cell suspensions, varying in concentration from 0.1 to 20%. These suspensions were prepared from a sarcoma that had been originally induced by methylcholanthrene in an animal of the same line. The Minimum Tumor Dose (MTD) capable of producing tumors in a majority of the inoculated animals was thus determined (0.02 cc. of a 0.5% suspension of tumor cells). The incidence of spontaneous regression of the intradermal tumors was inversely proportional to the inoculated dose. Thus 25 of 38 mice, *i.e.,* 66%, recovered from tumors that resulted from inoculation of 1 to 2.5 MTD of sarcoma (0.02 cc. of cell suspensions varying in concentration from 0.5 to 1.25%). On the other hand, only 11 of 43 mice, *i.e.,* 26%, recovered from tumors that resulted from inoculation of 20 to 40 MTD of sarcoma (0.02 cc. of 10 and 20% suspensions).

Of the 47 animals that had recovered from intradermal tumors 45 survived a second intradermal inoculation of sarcoma. These 45 mice were submitted to a subcutaneous test inoculation of the same tumor. None of the 5 immunized males resisted the test inoculation of 5,000 MTD, and 6 of 19 immunized males developed tumors following test inoculations of doses varying from 2 to 250 MTD of sarcoma. Two of 5 immunized females resisted the test inoculations of 5,000 MTD, and 16 females proved refractory to doses varying from 2 to 800 MTD of sarcoma. Fifty-one normal males and females of the same line were inoculated as controls with equal or smaller amounts of the same tumor cell suspensions, and all but one developed tumors.

These experiments suggest that accurate dosage is important in the study of tumor immunity, and that resistance acquired against neoplasms can be overwhelmed, especially in males, with massive doses of the tumor suspensions.—Author's abstract.

Attempts to Abrogate Immunity to the Brown-Pearce Carcinoma. Saphir, O., and Appel, M. [Michael Reese Hosp., Chicago, Ill., and Burnham City Hosp., Champaign, Ill.] *Cancer Research,* **3**:767-769. 1943.

Rabbits were immunized to the Brown-Pearce carcinoma by intracutaneous transplantation of this tumor. Attempts were then made to break down the immunity by blockade of the reticuloendothelial system. This was accomplished by prolonged intravenous administration of trypan blue; 7 of 9 tumor-immune animals thus treated developed tumor. The relationship of the reticuloendothelial system to the formation of tumor antibodies is discussed.—Authors' abstract.

The Heterologous Transplantation of Embryonic Mammalian Tissues. Greene, H. S. N. [Yale University Sch. of Med., New Haven, Conn.] *Cancer Research,* **3**:809-822. 1943.

A series of homologous and heterologous embryonic transplantation experiments is reported. It was found that rabbit embryos, either in whole or in part, could be readily transplanted to the anterior chambers of the eyes and to the testicles of other rabbits or guinea pigs. The resulting growths resembled teratomas and could be transferred serially. Similar results were obtained with human and

mouse embryonic material transplanted to the eyes of rabbits and guinea pigs. Organ transplants in both homolgous and heterologous species underwent differentiation and resembled mature structures. A variety of embryonic human organs including heart, lung, brain, stomach, intestine, and kidney were successfully transplanted, but all attempts to transfer liver or the organs of internal secretion failed.—Author's abstract.

Cytoplasmic Changes in Rous Sarcoma Cells Cultivated in Vitro. DOLJANSKI, L., and TENENBAUM, E. [Hebrew Univ., Jerusalem, Palestine] *Proc. Soc. Exper. Biol. & Med.*, **52**:267-269. 1943.

In tissue culture, the cytoplasm of the cell center at first becomes cloudy and finally assumes a very sharp outline. This segregated central area is 3 to 6 times the size of the nucleus, is sperical in shape, and always appears to be denser than the surrounding cytoplasm, but exhibits no pronounced structural peculiarities. The nucleus lies practically always outside the central area; in binuclear cells the central area is situated between the two nuclei.

The peripheral cytoplasm of the sarcoma cell is sharply marked off from the central region and has a flat membrane constantly changing in outline. Pseudopodia extruded by these cells appear as coarse rigid rods which move in all directions on their bases. The distal ends of these pseudopodia at times swell into spherical protoplasmic balls that float on their stems and often become detached.

Networks of thick or thin rods and granules staining intensely blue with Giemsa, appear to be hypertrophic mitochondria.

These changes are accompanied by definite hypertrophy of the involved cells.—M. B.

Rhabdomyosarcoma. Rat Tumor 92, Institute of Cancer Research, Columbia University, New York. LEWIS, W. H. [Carnegie Inst. of Washington, and Wistar Inst., Philadelphia, Pa.] *Cancer Research*, **3**:867-871. 1943.

This tumor, originally a chondrorhabdomyosarcoma, lost the chondrogenous part after a few rat-to-rat transfers and years later the muscle elements also disappeared. Malignant cells, obtained from a tumor without recognizable muscle, produced after 3 to 6 months' cultivation in roller tubes pure colonies of cells that gave rise, when inoculated into rats, to tumors with few to many muscle giant cells. After 400 to 600 days' cultivation the cells produced tumors but no giant cells. The malignant cells, probably myoblasts, regained on cultivation and then lost, perhaps temporarily, their ability to form giant cells. The living malignant cells in hanging drop cultures from all tumors and from tube cultures up to 3½ years' cultivation, were essentially alike, except for the usual variations.—Author's summary.

Polytene Chromosomes in Two Mammary Carcinomas of the Human Subject. BIESELE, J. J., and POYNER, H. [Univ. of Texas, Austin, and Houston, Tex.] *Cancer Research*, **3**:779-783. 1943.

Two mammary carcinomas of the human subject were found to contain chromosomes of 2 and 4 times the volume of those of granulation tissue, as well as chromosomes of the same size as those in normal tissues. The 3 sizes of chromosomes in the cancers gave rise to 3 sizes of nuclei. Probably the different nuclear classes in normal tissues are chiefly the result of polyploidy, but no polyploidy was found in the 2 cancers examined. Since there was an increase in the maximum nucleolar number with increase in size of the resting nucleus in the cancers, the enlarged chromosomes must have been many-stranded. Such polytene chromosomes were more frequent in the more malignant of the 2 carcinomas.—Authors' abstract.

Lung Tumors Following Intraperitoneal Injection of 1:2:5:6-Dibenzanthracene into Young Mice of Three Strains. LYNCH, C. J. [Rockefeller Inst., New York, N. Y.] *Proc. Soc. Exper. Biol. & Med.*, **52**:368-371. 1943.

The Swiss strain, the Rockefeller branch of the Bagg albino strain, and strain 1194 were used. The Swiss mice have the highest spontaneous lung tumor incidence (46%), that of the Bagg strain is less high (26%), and that of strain 1194 is least (5%). Lung tumors were induced by a single intraperitoneal injection of 0.125 mgm. of dibenzanthracene (0.5 minim of a 0.4% solution in olive oil) into mice 2 to 4 days old. Counts were made of the nodules seen on the surface of the lung with a dissecting microscope. The Swiss and Bagg strains attained an incidence of 100% tumor mice, but the Swiss mice had many more tumor nodules per lung. Strain 1194 attained an incidence of 52% with very few nodules per individual. The induced lung tumors appeared at a much earlier age than do spontaneous tumors. It is concluded that degree of susceptibility to induced lung tumor is inherited, and that 3 or more genes must be involved.—M. B.

The Inheritance of Tumors in Drosophila melanogaster with Especial Reference to an Isogenic Strain st sr Tumor 36a. RUSSELL, E. S. *Genetics*, **27**: 612-618. 1942.

Genetic as well as nongenetic influences operate in the development of tumors in *Drosophila melanogaster*. In the *st sr* stock several factors have been demonstrated. Essential is a recessive gene, or genes, on the second chromosome. Provided the second chromosome genes are present, those carried on the X chromosome may increase the incidence whereas the net effect of the third chromosome would be to decrease the incidence of tumors.—J. J. B.

Carcinoma of the Thyroid: A Report of Five Cases in Dogs. MCCLELLAND, R. M. [Buffalo, N. Y.] *J. Am. Vet. M. A.*, **98**:38-40. 1941.

All tumors were definitely malignant with many metastases to the lungs in each instance. Secondary nodules were found in the liver of 1 dog, in the kidney of 2 dogs, and a mass occurred in the mediastinum of one. Additional findings in individual cases were hydrothorax, cirrhosis of the liver, and hematoperitoneum following rupture of a renal metastasis. All 5 dogs were 8 or more years old. Four were females, 1 a male.—E. E. S.

Clinical and Pathological Reports

Therapy—General

The Value of the High Frequency Currents in Cancer Surgery. de Cholnoky, T. [New York, N. Y.] *M. Rec.*, **153**:187-189. 1941.

In general, electrocoagulation has no advantage over removal of a tumor by scalpel. Electrocoagulation controls hemorrhage better but recurrence is more frequent. This technic is useful, however, in the removal of precancerous cutaneous lesions and in the treatment of very extensive lesions of skin and mucous membranes. Delayed healing and tissue necrosis are possible postoperative complications of electrosurgery. Occasionally the author found it to be the method of choice in treating large infected "inoperable" malignant tumors for palliative effect.—E. E. S.

Radiation—Diagnosis and Therapy

Treatment of Cancer by Fast Neutrons. Gray, L. H., and Read, J. [Mount Vernon Hosp. and Radium Inst., Northwood, Middlesex, England] *Nature, London*, **152**: 53-54. 1943.

The paper is concerned with the differing biological effects of various radiations, particularly gamma rays, x-rays, neutrons, and alpha particles, in respect of the ion density of the ionization produced by them. It has now been established beyond doubt that the biological effect produced by ionizing radiations depends not only on the total ionization produced in the cell but also on the spatial distribution of these ions. Gamma rays produced about 10 ions per micron of track, 200 kv. x-rays produced 40, neutrons 500, and alpha particles 4,000. It has been found in certain cases, such as the production of sex-linked mutations in Drosophila sperm, the inactivation of a number of viruses, and the disinfection of vegetative bacteria, that the biological effect of the same total ionization depends upon the ion density; for example, in the effects noted above the efficiency decreases with increasing ion density. On the other hand, in the production of chromosome aberrations, the lethal effects on roots and shoots of seedlings, and a number of other reactions, the reverse change with ion density is observed. It is shown that the relative action on mouse tumor tissue irradiated *in vitro* is similar to that observed on the roots of *Vicia faba*, the efficiency increasing rapidly with ion density. Stone and Larkin formed an estimate of the relative effectiveness of neutrons and x-rays for the production of erythema of the skin, and the curve follows closely the action on the tumor. Any superiority of neutrons over x-rays may be taken to indicate that the relative efficiency is increasing more rapidly with ion density for the tumor than for normal tissues, and it is suggested by the authors that the neutrons from the 37 inch cyclotron or (D-D) neutrons would show an even greater superiority. It might be of therapeutic value to slow down the neutrons by passage through wax before entry into the body. Suggestions are made as to the choice of neutrons of optimum energy. When the 60 inch cyclotron is used it is likely that the skin is in a relatively favorable position, being exposed to very fast neutrons, and the tissues deeper than the tumor, being exposed to slow neutrons, are relatively more damaged than the normal tissue at the site of the tumor.—W. V. M.

The Measurement of Non-Ionizing Radiations for Medical Purposes. Mayneord, W. V., and Tulley, T. J. [Royal Cancer Hosp. (Free), London, England] *Proc. Roy. Soc. Med.*, **36**:411-422. 1943.

The paper contains an account of theoretical and experimental work on the measurement of nonionizing radiations, particularly infra-red and visible light. Reasons are given for suggesting that the incident intensity of radiation in therapeutic practice should be measured in gm. cal./cm.^{2} min. From such data energy absorption in the patient may be approximately deduced. The absorption in celluloid of radiation from sources of different color temperatures may form the basis of a "quality" measurement of infra-red.

The standards of radiation measurement employed are a Moll microthermopile with a fluorite window, calibrated by the National Physical Laboratory, and a 40 watt carbon filament lamp calibrated at the National Bureau of Standards, Washington. The 2 calibrations are in agreement. Small vacuum thermocouples have been used in the construction of a clinical instrument whose characteristics were carefully studied.

Measurements on patients show that the intensities of radiation employed in practice are frequently of the order of 2 gm. cal./cm.^{2} min. The threshold for pain appears to be 3 to 4 gm. cal./cm.^{2} min. The distribution of radiation over a plane perpendicular to the axis of the beam has been studied as well as that over the surface of patients being treated in radiant heat cradles. A study was also made of the variation of intensity with distance from a lamp in a reflector. The paper concludes with a discussion of total energy absorption and the most appropriate quantities to measure in practice.—W. V. M.

The Management of the Cancerous Patient under Radiation Therapy. Peirce, C. B. [Royal Victoria Hosp., Montreal, Canada.] *Canad. M. A. J.*, **47**:119-123. 1942.

A general discussion of the problems which confront the surgeon and the physician in the detection and treatment of cancer. The economic status of the cancerous patient is not negligible since, in many instances, it will determine whether the patient will seek early and proper advice. Among the problems that will arise are the expense of hospitalization, detailed clinical and laboratory studies, surgical intervention, radiation therapy at a properly equipped center, special diet, and nursing care. With women there is the problem of the care of the home and children, and in the case of men, provision for support of the family.

The body of the paper is concerned with the general and local treatment of cancer, and points of practical import are discussed in connection with each type of tumor. The problems that arise during roentgen therapy are reviewed and proper suggestions are offered. The point that the treatment of cancer and the management of the patient is a joint problem, is emphasized.—A. C.

Nervous System

Some Pathological Features of Primary and Secondary Extramedullary Tumors of the Spinal Cord. Elsberg, C. A. [Third International Cancer Congress, Atlantic City, N. J.] *J. Mt. Sinai Hosp.*, **7**:247-258. 1941.

In a series of histologically verified primary and secondary tumors of the spinal cord, there were 267 cases of extramedullary tumor. The perineurial and meningeal fibroblastomas comprised 46% of all the growths and 68% of intradural growths. Of the extradural growths, primary sarcoma was among the most frequent. Since the majority of patients with metastatic spinal disease are not operated upon, the number of extradural growths was relatively small. In general, the relative frequency of the various tumors at different levels of the spinal cord corresponded to the relative lengths of the cervical, thoracic, and lumbar segments. However, the incidence of meningeal fibroblastomas in the thoracic region was much higher than would be expected from the relative length of the thoracic segment. It is suggested that the frequency of meningeal growths in the thoracic region is related to the development of the spinal membranes. There is an increase of vascularity in the soft paravertebral tissues and in the bone, in vascular tumors of the spinal cord. The pathologic changes produced in the vertebrae and in the spinal cord by tumors are described.—A. Cnl.

Primary Neuroectodermal Brain Tumors; Their Transition from Benign to Malignant Forms. Globus, J. H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:361-382. 1941.

The present study supports accumulating evidence that brain tumors, as do tumors elsewhere, consist of cells that recapitulate morphologically one or another histogenetic phase of the primordial cells that serve as the germinal center of the tumor. The paper is especially concerned with a group of gliogenous tumors whose early stages presented a relatively benign character. In the course of their growth, these tumors changed into more malignant forms, taking on the anatomical character of primary malignant brain tumors such as are now termed spongioblastoma multiforme and spongioneuroblastoma. This transition may be observed by studying tumor tissue removed at repeated intervals in instances in which recurrence of the growths demands further operation. The suggested explanation of the transition from a benign to a malignant tumor is based on the Cohnheim-Ribbert embryonal rest theory. The influence of radiotherapy on such change is briefly discussed and considered to be of doubtful importance.—A. Cnl.

Cystic Tumor of the Fourth Ventricle. Zucker, J. M., and Mindlin, E. P. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **8**:92-95. 1941.

A case of a fourth ventricle tumor in a boy 13 years of age is presented. The tumor, a cystic hemangiomatous meningioma, was successfully removed at operation. The patient is apparently completely cured. The lesion is one of a group that offers the best opportunity for successful surgical intervention. Statistics supporting this view are presented—A. Cnl.

Breast

The End Results of Surgery in Breast Cancer. Bainbridge, W. S. [New York, N. Y.] *M. Rec.*, **153**:353-359. 1941.

The various types of therapy: surgery, radium implantation, x-rays, and combinations of these are discussed. The author feels strongly that radical surgical removal of the breast and invaded areas without irradiation is the best means of cure, provided a careful technic is followed. The operative methods of the author are set forth in detail. A brief summary of 51 cases with pathologic reports and time of survival is included.—E. E. S.

Stilboestrol for Breast Tumour. Biden, W. M. [Pitlochry, England] *Brit. M. J.*, **2**:57. 1943.

In a letter to the Editor, Biden reports the case of a woman of 78 years of age who for 10 years had had a tumor in the upper and outer quadrant of the left breast. Latterly the tumor was offensive and fungating, and appeared to be an adenocarcinoma. There were enlarged nodes in the axilla. Treatment was begun with diethylstilbestrol, in 1 mgm. doses thrice daily to a total of 250 mgm. One month later the tumor appeared to be slightly smaller, and the patient was improving in health. After 3 months the tumor was decidedly smaller, and covered by a thin layer of epithelium. Regression continued, and at the time of writing, 6 months after commencement of treatment, there was a firmly healed nonadherent scar, measuring 3 by 1½ inches, at the site of the tumor.

It was unfortunate that biopsy material could not be obtained.—A. H.

Female Genital Tract

Sarcoma in Fibromyoma of the Uterus. Goldberger, M. A. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:383-390. 1941.

Myomectomy, if done early, may eradicate fibromyoma, but sarcoma of the uterine wall and of the endometrium requires radical operative removal. Sarcoma in a fibromyoma gives no characteristic symptoms except when extensive involvement is present. A review of 2,916 cases of fibromyoma in which surgical intervention was performed at this hospital from 1933 to 1940 revealed 29 proved cases of sarcoma, an incidence of 0.48%. This is lower than the figure of 2.1% given in the literature. The histological classification of sarcoma is described according to the morphology and genesis of the tumor.

Two cases are reported in which the tumor proved to be sarcoma although the myomectomy was performed for a benign fibromyoma. The 2 patients were apparently cured.—A. Cnl.

Male Genital Tract

The Ratio of Urinary Androgen and Estrogen in Relation to Benign Hypertrophy of the Prostate. Miller, M. L., and Moore, R. A. [Washington Univ. Sch. of Med., St. Louis, Mo.] *J. Urol.*, **49**:861-864. 1943.

The authors indicate that a minor alteration in the ratio of estrogen and androgen could give an estrogenic preponderance even though no excess of estrogen alone be

found in the urine. The estrogen–androgen ratio was determined over a period of 30 days on 2 aged males, one with, and one without, clinical evidence of benign hypertrophy. The average ratio was 3 times greater in the patient with benign hypertrophy. The authors state that further studies in this direction are needed.—V. F. M.

Hipertrofia de la próstata, Consideraciones sobre el adenoma de la próstata. [Hypertrophy of the Prostate, Considerations on Adenoma of the Prostate.] TRABUCCO, A. [Buenos Aires, Argentina] *Rev. Asoc. méd., argent.*, **55**:98-106; 455-456. 1941.

The author discusses the etiology and pathogenesis of the tumor; the physiopathology of urine retention; and the results of endocrinotherapy in adenoma of the prostate. He favors the theory of lack of balance in testicular hormone as the etiological factor and is of the opinion that these adenomas should be regarded as benign growths that readily become malignant. In this connection the author quotes the statistics of Albarran and Hallée in which 14% of the adenomas showed centers of carcinomatous degeneration, and those of Chauvin and Messinger in which 32% showed metaplasia and some true spindle cell carcinomas. Destruction of muscle in the bladder is often connected with urine retention.

Testosterone propionate was given to 50 patients, the optimum dose averaging 167 mgm. The symptoms began to subside after an average of 10 to 15 days. If treatment was stopped after the maximum improvement was reached, the symptoms reappeared after an average interval of 30 days. The minimum dose necessary to maintain the improvement was 5 mgm. a week. Dysuria subsided quickly in 21% of the cases, gradually in 15%, slowly in 10%, and hardly at all in 15%. Polyuria disappeared completely in 30% of the patients, was reduced to 1 micturition per night in 23%, and to 2 or more in 15%. Urine retention was completely relieved in 52%, but in these cases it had been mild in the beginning; in the remaining patients it was reduced to half that which it had been before treatment. Endocrinotherapy does not seem to affect the size of the tumor and does not change the symptoms in the second or third phase of the disease. Fourteen illustrations are appended.—M. D-R.

URINARY SYSTEM—MALE AND FEMALE

Hypernephroma of the Kidney. With Solitary Metastasis to the Cerebellum. EDELMAN, L. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:343-348. 1941.

Although the usual presenting symptoms of hypernephroma of the kidney are referable to the urinary tract, not infrequently the first symptom to attract attention is not from the primary tumor, but from a distant metastasis. The present case is of particular interest because the first sign was a metastatic tumor removed from the cerebellum. Since no other metastases were demonstrable, a nephrectomy was performed 6 weeks later. The patient is now alive and well 2 years after operation. There is no doubt that a fairly large percentage of renal tumors escape early detection. In 41% of 92 cases reviewed by Creevy, the presenting symptoms were outside the urinary tract. The pyelogram is the only basis on which the diagnosis can be made with reasonable certainty. Nephrectomy offers the best hope for a cure. A solitary metastasis is no contraindication to operation and should be removed if accessible. X-ray therapy has little or no value in hypernephroma.—A. Cnl.

The Diagnosis of Bladder Neoplasm in Benign Prostatic Hypertrophy. HYMAN, A., and LEITER, H. E. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:426-431. 1941.

Bladder neoplasm associated with benign prostatic hypertrophy is not rare. As a rule this tumor is readily detected by cystoscopic examination. Although hematuria is the cardinal symptom of neoplasms of the bladder, it is also commonly associated with prostatic hypertrophy. Thus, a neoplasm can easily be overlooked in patients with marked hypertrophy of the prostate. The first diagnostic procedure should be excretory urography. Cystography is the next step, with anteroposterior, oblique, and aerogram exposures, and varying strengths of radiopaque media. A complete cystoscopic examination should be carried out. The authors present 4 cases that illustrate the problems involved.—A. Cnl.

Primary Carcinoma of the Ureter. MCCREA, L. E. [Temple Univ. Med. Sch., Philadelphia, Pa.] *Urol. & Cutan. Rev.*, **46**:485-490. 1942.

A brief review of the literature is given covering 161 reported cases. Two additional instances are here described. In each of the latter, by means of the cystoscope the tumor could be seen protruding from the ureteral orifice. One patient died before specific therapy could be given. Partial autopsy revealed no metastases, but the kidney was destroyed. Most of these tumors are papillary carcinomas, but squamous cell carcinoma and one primary sarcoma have been reported. The majority of tumors occur in the fifth and sixth decades of life. Surgical removal is the treatment of choice.—V. F. M.

INTRATHORACIC TUMORS—LUNGS—PLEURA

Benign Adenoma of the Bronchus. KRAMER, R. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:443-444. 1941.

Approximately 7% of all bronchial tumors are benign adenomas; the remainder are malignant growths of various types. The treatment of the benign tumor is bronchoscopic removal, usually in combination with surgical diathermy, occasionally with implantation of radium, and rarely with external roentgen ray therapy. Early diagnosis results in complete cure without residual pulmonary changes. In the case reported herein, the patient was restored to good health within a short period by 3 bronchoscopic procedures carried out under local anaesthesia. Asthma, which had been present for many years, disappeared with the removal of the tumor.—A. Cnl.

GASTROINTESTINAL TRACT

The Problem of Cancer of the Esophagus. GARLOCK, J. H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:349-352. 1941.

Rapid progress is being made in the treatment of a disease heretofore considered to be hopeless. It is now pos-

sible to assure the patient with cancer of the esophagus of a reasonable chance of survival. The author reports 20 cases in which operation for squamous cell carcinoma of the esophagus was performed during the past 4½ years. Fourteen patients were found to present operable lesions, an operability rate of 70%. In this group of 14 patients subjected to radical resection, there were 5 deaths, an operative mortality of 36%. Of the 9 survivors, 5 are alive and well, 1 after almost 4 years. The remaining 4 patients died of local recurrence or other causes. In contrast with this is a group of 15 patients who were operated upon for adenocarcinoma of the cardiac end of the stomach and esophageal obstruction. Only 5 presented operable lesions, an operability rate of 33%. Two patients subjected to resection with intrathoracic esophagogastric anastomosis succumbed, and 3 survived and are well. One has lived 14 months after operation.

In operating, the transpleural approach was employed, and an attempt was made to construct subsequently a skin-lined tube on the anterior chest wall to replace the resected esophagus. Until recently, it was thought necessary to perform gastrostomy preliminary to resection of growths in the middle third of the esophagus. To obviate this, the author performed an esophagostomy and preserved the sphincteric mechanism of the cardia of the stomach. In the ideal case, when the tumor is in the lower third of the esophagus, esophagogastric continuity is reestablished by anastamosis. It is important for the esophagoscopist to locate accurately the position of the neoplasm as it helps the surgeon to decide which procedure to use.—A. Cnl.

Carcinoma of the Anus Treated by Radiation Therapy. Harris, W. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:405-410. 1941.

Among 534 patients with neoplasm of the lower bowel, seen at The Mount Sinai Hospital from 1933 to 1940, there were 5 with verified carcinoma of the anus, an incidence of 0.84%. Of the anal lesions, 1 was a basal cell carcinoma, and 4 were squamous cell carcinomas. The basal cell lesion was treated by excision and cauterization; the squamous cell carcinomas were treated by roentgentherapy, usually by external irradiation only, but in one instance by interstitial radon as an adjuvant. Treatment was contraindicated in one case because of glandular involvement. An adenocarcinoma found at biopsy is usually of rectal origin.—A. Cnl.

Blood Histamine in Gastric Cancer and Peptic Ulcer. Shimkin, M. B., Zon, L., and Crigler, C. W. [Marine Hosp., Baltimore, Md.] *Proc. Soc. Exper. Biol. & Med.*, **52**: 335-338. 1943.

It has been reported that peptic ulcers have been produced in experimental animals injected with histamine, and that there is a gastric secretory depressant in the extracts of achlorhydric cancerous stomachs and in juices from such stomachs. The blood histamine in patients with gastric carcinoma and with peptic ulcer was between 1.2 γ and 8.5 γ per 100 cc. There was no difference between the two groups, and no significant deviation from the normal range (reported as 1.8 γ to 7.8 γ). There was no relationship between blood histamine and the presence or absence of free HCl in the stomach. Blood histamine in man is carried chiefly by granulocytes, but is not directly related to the number of granulocytes in the blood.—M. B.

Lymphosarcoma of the Stomach. Yarnis, H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **8**:305-307. 1941.

One thousand and thirty-five cases of neoplasm of the stomach were diagnosed in The Mt. Sinai Hospital from 1933 to 1940. There were 12 lymphosarcomas, an incidence of 1.2%. It is important to differentiate this type of tumor from carcinoma because surgery offers a better prognosis for it in the early stages of the disease, while for the advanced or inoperable lesions, radiotherapy is definitely indicated. It is impossible to make a clinical diagnosis of lymphosarcoma with certainty, but in the case reported, lymphosarcoma was suggested by roentgenologic and gastroscopic studies. If possible, resection of the tumor should be performed, since the disease remains localized to the stomach for a relatively long time. In inoperable lesions radiotherapy has proved of definite value in relieving symptoms, prolonging life, and perhaps, effecting a permanent cure.—A. Cnl.

Liver

La bilirrubina eteroextraible en los neoplasmas de las vias biliares. [Ether-Extractable Bilirubin in the Neoplasms of the Bile Ducts.] Franchi, P. H., and Graña, A. [Montevideo, Uruguay] *Arch. urug. de med., cir. y especialid.*, **19**:293-296. 1942.

In certain icteric sera a bilirubin that could not be extracted with chloroform was found. The authors called this compound "ether-extractable bilirubin" and observed that in 80% of the cases it was associated with neoplasms of the bile ducts. Three cases are presented in which such findings are confirmed. The first case showed large amounts of "ether-extractable bilirubin" in the serum 2 days after the appearance of jaundice. Postmortem examination revealed a sarcoma of the testicle with metastasis in the liver and the bile ducts, and a neoplastic bladder with thickening of the walls. The second case showed 1.34 mgm.% of the substance 15 days after the appearance of jaundice. Postmortem examination showed a neoplastic bladder filled with gallstones, and neoplastic bile ducts. The third case showed 1 mgm.% of bilirubin 10 days after the appearance of jaundice. This patient is still alive, and the diagnosis is probable neoplasm of the head of the pancreas. If the diagnosis proves to be correct, this will be the third reported case of "ether-extractable bilirubin" with this type of neoplasm. The authors mention a fourth case of jaundice with a neoplasm of the gall bladder where "ether-extractable bilirubin" was not present. The jaundice was caused by a gallstone in the bile ducts, but the bile flow did not come in contact with the neoplastic walls.

Experiments were carried out in which icteric serum from a patient with catarrhal jaundice was mixed with fragments of tumor in order to see if contact with the latter would cause the appearance of "ether-extractable bilirubin" in the serum. The results were negative, and the authors conclude that the presence of this type of bilirubin might be a result of lipoproteic changes of the icteric serum.—M. D-R.

Muscle and Tendon

Malignant Tumors of Synovial Origin. Briggs, C. D. [Washington, D. C.] *Ann. Surg.*, **115**:413-426. 1942.

Synovioma is defined as a malignant tumor arising from the joint capsule, bursal wall, or tendon sheath. Nine case studies are submitted. The clinical and pathologic manifestations of this infrequently diagnosed group of tumors is discussed. Treatment by complete surgical excision or amputation is recommended.—M. R. D.

Tumors of Tendon Sheaths. Charache, H. [Brooklyn, N. Y.] *Arch. Surg.*, **44**:1038-1052. 1942.

The author has made a comprehensive survey of the literature on tendon sheath tumors and suggests a classification of benign tumors of this origin in the following divisions: ganglion, xanthomatous giant cell tumor, lipoma, hemangioma, lymphangioma, fibroma, and osteochondroma. The malignant tumors are: synovioma, spindle cell sarcoma, and chondrosarcoma. Pathology, diagnosis, treatment, and prognosis are considered in each category. Five case reports are presented.—R. C. R.

Desmoid Tumors. Pearman, R. O., and Mayo, C. W. [Mayo Clinic, Rochester, Minn.] *Ann. Surg.*, **115**:114-125. 1942.

A clinical and pathologic study of 77 instances of desmoid tumors seen over a 30 year period. The lesions are defined as benign fibromas arising from musculo-aponeurotic structures. They occur most frequently in the musculature of the anterior abdominal wall. The etiology is not known. Treatment consists of complete excision.—M. R. D.

Blood Vessels

A Case of Associated Facial and Intracranial Hemangioma. Shapiro, L. B. [Northwestern Univ. Med. Sch., Chicago, Ill.] *Illinois M. J.*, **83**:272-274. 1943.

A case recording the pertinent clinical findings of facial nevus on the left side, calcifications in the occipital cortex, localized Jacksonian convulsive seizures involving the right lower extremity, and urinary incontinence.—M. E. H.

Hemangiopericytoma of the Omentum. Stout, A. P., and Cassel, C. [Coll. of Physicians and Surgeons, New York, N. Y., and Jackson Mem. Hosp., Miami, Fla.] *Surgery*, **13**:578-581. 1943.

A case report.—W. A. B.

Adrenal

Pheochromocytoma of the Adrenal Gland. Hyman, A., and Mencher, W. H. [Mt. Sinai Hosp., New York, N. Y.] *J. Urol.*, **49**:755-776. 1943.

Thirty-five instances of operative removal of pheochromocytoma of the adrenal gland are reported in the literature. A typical history consists of attacks of paroxysmal hypertension and other indications of hyperadrenalinism. Pressor substance is demonstrated in the blood and in the tumor tissue. Diagnosis depends on symptomatology, typical pressor response mechanisms, the demonstration of pressor subtance in the blood during the attack, and the demonstration of tumor by perirenal insufflation x-rays. The authors report 4 cases with successful operative removal of the tumor. In the discussion 3 cases are added.—V. F. M.

Pituitary

The Management and Treatment of Pituitary Tumors. Adelstein, L. J. [Univ. of Southern California Sch. of Med., Los Angeles, Calif.] *West. J. Surg.*, **50**:230-237. 1942.

Irradiation of pituitary adenomas may well be tried first—before surgical intervention—unless there are special contraindications such as progressive and imminent loss of vision. Postoperatively, roentgen therapy seems definitely to prolong the period before evidence of recurrence appears.—M. E. H.

Adenoma of the Pituitary Simulated by a Cranio-Pharyngeal Neoplasm. Coon, W. L. [Veterans' Administration, Wood, Wis.] *M. Bull. Vet. Admin.*, **19**:458-459. 1942-43.

A case report.—M. E. H.

Tumors of the Pituitary Gland. Cranmer, R. R. [Minneapolis, Minn.] *Minnesota Med.*, **25**:38-42. 1942.

Diagnosis of primary hypophysial tumors is based on: (1) endocrine disturbances; (2) changes in the bones, as evidenced by radiograms, such as enlargement and destruction of the sella turcica, and occasionally an intrasellar shadow; (3) changes in visual fields and eyegrounds; (4) headaches and other signs of increased intracranial pressure.

These tumors are treated by surgical intervention and x-ray. Four cases are presented.—J. L. M.

Thyroid

Operation for Carcinoma of the Thyroid of Lateral Aberrant Origin. Cattell, R. B. [Lahey Clinic, Boston, Mass.] *Surg. Clin. North America*, **22**:681-685. 1942.

All patients with lateral aberrant thyroid nodules should be operated upon. If the tumor appears to be discrete and single, its removal together with the lymph nodes immediately adjacent can be carried out. If the lymph nodes are not involved and the homolateral lobe of the thyroid gland has no involvement, this procedure should give a good result. If multiple nodules are present, or if the thyroid lobe on the same side of the neck is involved, a more radical operation is indicated. Under these circumstances a diagnosis of carcinoma of the thyroid of lateral aberrant thyroid origin must be made. A radical dissection of the neck, particularly of the lower two-thirds, should be carried out in the presence of these findings, and postoperatively these patients should receive adequate x-ray therapy.

The technic of the procedure employed by the author is outlined.—J. L. M.

Lateral Aberrant Thyroids. Frantz, V. K., Forsythe, R., Hanford, J. M., and Rogers, W. M. [Coll. of Physicians and Surgeons, and Presbyterian Hosp., New York, N. Y.] *Ann. Surg.*, **115**:161-183. 1942.

Lateral aberrant thyroids are defined, and their embryological development is discussed with reference to surgical, anatomic, and pathologic findings. Thirty case studies are analyzed. The authors emphatically state that all lateral aberrant thyroid masses should be considered potentially malignant, be studied with care, treated radically, and followed indefinitely.—M. R. D.

MISCELLANEOUS

Lipoma of the Mesentery in a Child Aged Two Years. BASS, M. H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **7**:298-306. 1941.

Tumors of the mesentery are of rare occurrence, especially in children. They may be divided into the cystic and the solid types, the former being more commonly encountered. The solid tumor arises from the connective tissue between the mesenteric leaves and may therefore appear as fibroma, lipoma, fibromyoma, or sarcoma. It is often the seat of inflammatory and degenerative processes, sometimes giving rise to pseudocysts, thus leading to confusion in diagnosis. There are 23 reported cases of solid mesenteric tumors in children, with 10 recoveries, and 8 deaths. In 5 cases the outcome is not known. The treatment is surgical. Operation should be undertaken as soon as the diagnosis is made because the growth is malignant or may become so, and because intestinal obstruction may complicate the condition at any time. The symptomatology of these tumors is discussed, and a case is presented.—A. Cnl.

Salient Factors in the Diagnosis and Treatment of Cancer. BEHAN, R. J. [Pittsburgh, Pa.] *M. Rec.*, **154**: 326-332. 1941.

The influence of heredity on the development of cancer is briefly mentioned. The author believes trauma to be an important etiologic factor. The nutritional requirements of cancer cells are stated to be greatly in excess of those of normal cells, and ligation of the blood supply to the tumor is suggested as a means of reducing the rate of growth. Characteristics of the malignant form of growth such as invasion, necrosis, ulceration, and hemorrhage are discussed. Special mention is made of the particular features important for the diagnosis of carcinoma of the breast. X-rays are of particular aid in the diagnosis of carcinoma of the alimentary tract. The need for specific knowledge of the most effective means of therapy for individual tumors is stressed. There is a brief discussion of various means of alleviating pain.—E. E. S.

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VOLUME 3
NUMBER 12
DECEMBER, 1943

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OF ARTICLES AND ABSTRACTS
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AMERICAN ASSOCIATION FOR CANCER RESEARCH, INC.

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Published by The International Cancer Research Foundation.
Publication Office, 1500 Greenmount Ave., Baltimore 2, Maryland.

The annual subscription rates for one volume are: To members of the American Association for Cancer Research, Inc., $5.00; to others and to libraries, institutions, and organizations, $7.00. Business communications, remittances, and subscriptions should be addressed to Robert W. Briggs, Business Manager, 1500 Greenmount Ave., Baltimore 2, Md., or 2500 Lincoln-Liberty Building, Philadelphia 7, Pa.

No responsibility is accepted by the Committee, by the Board, or by the Publishers of *Cancer Research* for opinions expressed by contributors.

Entered as second class matter February 12, 1941, at the Post Office at Baltimore, Md., under the Act of March 3, 1879.

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REFERENCES. These should be arranged alphabetically by authors. For citation of a book, give name of author, complete title, place of publication, name of publisher, year, and page. For an article, name of author, full title of paper *exactly as it appears,* name of journal (abbreviated as in the *Quarterly Cumulative Index Medicus*), volume number, inclusive page numbers, and year. The following examples illustrate the desired punctuation and arrangement:

EWING, J. Neoplastic Diseases. A Treatise on Tumors. Fourth edition. Philadelphia & London: W. B. Saunders Company. 1940, p. 449.

SAPHIR, O., and PARKER, M. L. Intracystic Papilloma of the Breast. Am. J. Path., **16**:189-210. 1940.

SUMMARY. This should be an abstract of the whole paper, complete in itself, and limited to about 3 per cent of the length of the article.

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